INFLUENCE OF REDUCTION OF SERUM LIPIDS ON PROGNOSIS OF CORONARY HEART-DISEASE

A Five-year Study Using Œstrogen

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THE principal arguments for incriminating cholesterol in the ætiology of coronary atherosclerosis can be outlined as follows:

The earliest lesions in human coronary arteries are fatty streaks containing cholesterol esters (Klotz and Manning 1911, Holman et al. 1958), and with increasing atherosclerosis of the coronary arteries the content of cholesterol esters increases (Böttcher et al. 1960).

Since the pioneer experiments of Anitschkow and Chalatow (1913), it has been shown that fatty arterial lesions can be produced in many species by cholesterol feeding. The extent and degree of these arterial lesions can usually be related to the height and duration of the experimentally induced hypercholesterolæmia.

Patients with diseases which have little in common except hypercholesterolæmia—such as xanthomatosis, diabetes mellitus, myxœdema and certain kinds of nephrosis—often develop atherosclerosis in comparatively severe form early in life. Patients with overt features of coronary heart-disease often have higher serum-cholesterol levels than those without evident coronary disease, particularly men who develop coronary heart-disease in early middle age (Oliver and Boyd 1953, Biorck et al. 1957, Oliver 1958); and it has now been established that elevated serum-cholesterol levels *precede* the clinical development of coronary heart-disease and that people with high plasma-cholesterol levels have a greater risk of developing coronary heart-disease than those with lower levels (Cooperative Study of Lipoproteins and Atherosclerosis 1956, Dawber et al. 1957, Dawber 1961).

The associations of high serum-cholesterol levels with coronary heart-disease do not necessarily indicate any *causal* relationship. Nevertheless, many believe that hypercholesterolæmia contributes to the development of coronary atherosclerosis, and a great deal of research has been directed to the development of methods and regimes designed to reduce elevated serum-cholesterol levels in patients with coronary heart-disease. The assumption that reduction of elevated serum-cholesterol levels will improve prognosis has not yet been adequately tested. This paper describes a five-year investigation of the effect of the reduction of serum lipids, by the use of an œstrogen, on the prognosis of men surviving their first myocardial infarct.

Design of Study

Selection of Patients

Since the factors which determine the length of survival of a patient with manifest coronary heart-disease are not fully understood, it is wise to select for any prognostic study as homogeneous a group of the coronary population as can be found. By selecting such a group, or by studying very large numbers, some of the unpredictability of the prognosis of coronary heart-disease can be reduced.

The study began on July 1, 1953. In order to obtain 100 patients who were regarded as suitable for admission to the trial, the period of selection continued until July 12, 1955. All the men considered for selection were admitted to the same two medical wards of the Edinburgh Royal Infirmary within forty-eight hours of the *first* acute myocardial infarct. The criteria of acute myocardial infarction were the presence of Q waves (usually associated with ST shifts) and subsequently the presence of inverted T waves in the electrocardiogram. First myocardial infarction was said to be present when there was no clinical history and no electrocardiographic evidence of a previous myocardial infarct. Only men between the ages of 35 and 64 years were considered for the trial.

From July 1, 1953, to July 12, 1955, 186 men were discharged consecutively after twenty-four to forty-two days' hospital treatment for their first acute myocardial infarct. All received phenindione during recovery from acute infarction, but none had anticoagulant therapy after discharge from hospital. Selection and admission to the trial was made between three and four months after myocardial infarction, and during the interval between discharge from hospital and final selection for the trial 4 men died. At each of the three outpatient visits between the man's discharge from hospital and his admission to the trial, measurement was made of his weight, blood-pressure, serum-cholesterol, and serum-cholesterol/phospholipid (C/P) ratio. This period of three months before admitting the patient to the trial gave him time to return more or less to normal activity, allowed more accurate assessment of the criteria for inclusion (such as diastolic blood-pressure), and gave an opportunity for estimation of the pretreatment level of serum-cholesterol and C/P ratio independent of any effect that the acute myocardial infarct may have had. After the start of this trial, Biorck et al. (1957) and Dodds and Mills (1959) showed that an acute myocardial infarct produces a fall in the serum-cholesterol, which takes six weeks to return to the patient's usual level.

TABLE I—SELECTION OF PATIENTS

Total number of men aged 35–64 considered for study	182
Rejected from study:	
Hypertension (diastolic blood-pressure over 100)	26
Angina for more than six weeks preceding infarct	22
Severe congestive failure after myocardial infarct	17
Obesity (15% more than standard)	9
Hypercholesterolæmia (400 mg., or more, per 100 ml.)	3
Myxœdema	3
Diabetes mellitus	2
Accepted for study	100

From the remaining 182 men, 100 were selected for inclusion in this pilot trial of the effect on prognosis of reducing plasma-cholesterol; reasons for excluding 82 patients are shown in table I. There is adequate evidence in the literature that diastolic hypertension, obesity, and hypercholesterolæmia may worsen the prognosis. Thus, patients with a diastolic blood-pressure of more than 100, weight 15% in excess of their standard, or serum-cholesterol more than 400 mg. per 100 ml. were excluded. Patients who developed severe congestive failure were excluded, since congestive failure, even if treated successfully during the phase of recovery from the acute infarct, is likely to recur and affect the prognosis adversely.

The date of onset of angina is often difficult to define, and in order to make the length of history approximately comparable we decided to exclude all patients who had had angina for more than six weeks. Since recurrence of myocardial infarction in diabetic and myxœdematous patients is partly related to the degree of control of the underlying disease,

* This study was undertaken during tenure of a senior research fellowship in the department of cardiology, Royal Infirmary, Edinburgh.

TABLE II—SHOWING SIMILARITY OF CONTROL AND ŒSTROGEN-TREATED GROUPS

—	Control group	Œstrogen group
Total number of men	50	50
Diastolic blood-pressure (mm. Hg):		
Less than 70	4	2
70–80	12	11
80–90	23	22
90–100	11	15
Serum-cholesterol (mg. per 100 ml.):		
Less than 200	9	10
200–250	23	20
250–300	16	15
300–400	2	5
Weight (lb.):		
Less than 120	1	1
120–140	9	9
140–160	24	27
160–180	13	11
More than 180	3	2

5 patients with these conditions were also excluded. It was felt that exclusion of patients with these associated conditions left a reasonably homogeneous group of men for allocation to a treatment and a control group.

Selection of Treatment

As the means for lowering serum-cholesterol an œstrogen was selected mainly because, in 1953, œstrogens had produced a more consistent and significant fall in serum-cholesterol and β-lipoprotein cholesterol than any other agent tested. It was not until the latter part of 1954, and in 1955 and 1956, that the effect of reducing serum-cholesterol with vegetable oils was substantiated (Ahrens et al. 1954, 1955, Beveridge et al. 1955, Malmros and Wigand 1955, Bronte-Stewart et al. 1956). In contrast, several investigators (Barr et al. 1952, Barr 1953, Oliver and Boyd 1954, Steiner et al. 1955) had studied the effect on the serum lipids of administering œstrogens to men with coronary heart-disease. These studies generally confirmed the finding of Eilert (1949, 1953) who studied the effect of œstrogen administration on the serum lipids in normal women. Subsequent experiences (Oliver and Boyd 1956) indicated that, of various œstrogens, ethinyl œstradiol produced the most significant depression of serum-cholesterol with only moderate side-effects. Dose response curves of the effect of ethinyl œstradiol on serum-cholesterol and the C/P ratio indicated that a daily dose of 200 μg. was the optimum for long-term administration to men with coronary disease (Oliver and Boyd 1959). Despite the obvious disadvantages of their feminising action, œstrogens remain the most effective means of reducing the serum-cholesterol over a long period without modification of diet.

Procedure of Study

After three months' observation as outpatients, 50 men were given ethinyl œstradiol 200 μg. daily (œstrogen group) and 50 men tablets identical in shape and colour containing lactose (control group).

Patients were selected for the œstrogen group or control group alternately according to the date of their discharge from the ward. Since it was known that gynæcomastia would develop in the majority within three months, it was decided that there was no useful purpose in conducting a double-blind trial and thus the physician knew which patients were receiving ethinyl œstradiol and which were receiving lactose. There was no significant difference in the age-distribution between the two groups. Though the occupations of the men in the two groups varied considerably, this did not reflect any significant difference in social or economic background. There was no significant difference between the two groups in serum-cholesterol levels, diastolic blood-pressure, or weight (table II).

The patients of the two groups had the same routine and instructions. Men in the œstrogen group attended as outpatients on different days from men in the control group, so as to avoid waiting-room discussions. In certain men receiving ethinyl œstradiol the dose had to be increased in order to control the serum-cholesterol, and for every man whose dose of œstrogen was increased, a man in the control group was instructed to increase his dose of lactose. The patients' family doctors were kept fully informed of the trial. All men attended every three months during the first year of the trial and every six months during the next four years. They were always seen by the same physician (M. F. O.) and at each visit a physical examination was undertaken and measurements were made of the serum-cholesterol and C/P ratio, blood-pressure, and weight; at every second visit a 12-lead electrocardiogram was recorded. The men were instructed to take the diet to which they had been accustomed before their myocardial infarct. At the end of each year, a week's dietetic history was obtained; none of the 100 men made any significant change in the caloric value or animal and vegetable fat content during the five years.

The serum-cholesterol was estimated by the Sperry and Webb modification (1950) of the Sperry-Schoenheimer procedure. The plasma-lipid phosphorus was estimated by the molybdenum-blue method of Allen (1940). When estimations were made of lipoprotein cholesterol, this was done by the microzone paper electrophoretic method of Boyd (1955).

Results

Serum Lipids

As already indicated, all those selected had serum-cholesterol levels less than 400 mg. per 100 ml. The pretreatment level of the serum lipids was determined from three estimations taken at two or three weekly intervals following the patient's discharge from hospital.

Serum-cholesterol —During the two months between discharge from hospital and the start of the trial, the average mean serum-cholesterol level of the men later selected for œstrogen treatment was 238 mg per 100 ml., and of those later selected to receive lactose was 236 mg. Within three months of the start of the trial, the mean serum-cholesterol of the œstrogen group fell to 217±42 mg., in contrast with a mean serum-cholesterol in the control group of 232±37 mg. ($P < 0.001$)† (fig. 1.) Throughout the five years the mean serum-cholesterol of the œstrogen group remained significantly lower than that of the control group, and at the end of the fifth year was 198±40 mg. This represents a fall of 18%. In contrast, the mean serum-cholesterol level of the control group was 236±36 mg ($P < 0.001$.)

Since it could be argued that those patients with high serum-cholesterol levels might receive more benefit from cholesterol reduction than those whose serum-cholesterol was more normal, a separate analysis has been made of all men whose pretreatment mean serum-cholesterol levels were greater than 270 mg. per 100 ml. (This somewhat arbitrary figure of 270 mg. was derived from an earlier study of serum-lipid levels in 100 healthy men between the ages of 26 and 49; the mean serum-cholesterol in this group was 182±40 mg. Thus, the addition of two standard deviations to this mean gives a figure of 262 mg., and it was felt that the adoption of an arbitrary level of 270 mg would be acceptable for this purpose.) During the interval between discharge from the ward and the commencement of the trial, 17 men who were later to

†P values refer to differences between the means.

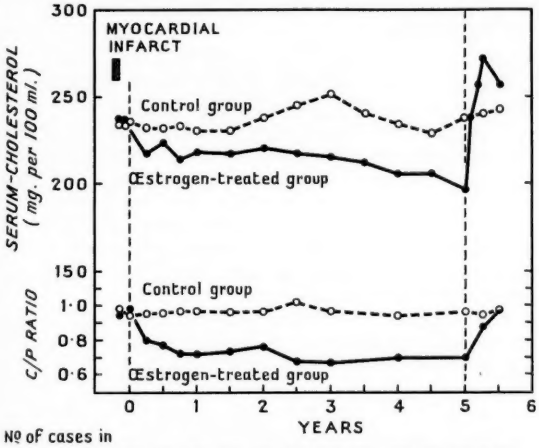

Fig. 1—Changes in the serum-cholesterol and C/P ratio during the 5-year study of 100 survivors of first myocardial infarction.

receive ethinyl œstradiol had a mean serum-cholesterol of 285 mg, and 16 who were later to receive lactose had a mean serum-cholesterol of 275 mg. Within three months the serum-cholesterol of the œstrogen group had fallen to 238 ± 42 mg., while that of the control group was 265 ± 26 mg ($P < 0.05$). Throughout the next five years the serum-cholesterol of the œstrogen group was significantly reduced, and by the end of the fifth year the mean serum-cholesterol of this previously hypercholesterolæmic subgroup of the trial was 196 ± 54 mg. This represents a fall of 33%. In contrast, the mean serum-cholesterol of the control subgroup was 269 ± 17 mg. ($P < 0.01$).

C/P ratio.—During the interval between discharge from the ward and commencement of treatment, those men later to receive œstrogens had a mean serum C/P ratio of 0·96 and those later to receive lactose had a mean serum C/P ratio of 0·94. Within three months of the start of the trial, the mean serum C/P ratio of the œstrogen group fell to 0.77 ± 0.13, while that of the control group was 0.95 ± 0.13 ($P < 0.001$). Throughout the five years the mean serum C/P ratio of the œstrogen group remained significantly lower than that of the control group, and at the end of the fifth year it was 0.70 ± 0.14. This represents a fall of 28%. In contrast, the mean serum C/P ratio of the control group was 0.99 ± 0.13 ($P < 0.001$).

The same general trend was true for the subgroup who were regarded as hypercholesterolæmic according to the definition already outlined. The pretreatment mean serum C/P ratio of the subgroup later to receive œstrogens was 0.98 ± 0.13, and within three months of the starting of treatment this had fallen to 0.78 ± 0.14, while that of the control sub-group was 0.99 ± 0.13 ($P < 0.001$). After five years the mean serum C/P ratio of the œstrogen group reached a level of 0·69. This represents a fall of 30%. In contrast, the mean C/P ratio of the control group was 0.97 ± 0.13 ($P < 0.001$).

Lipoprotein cholesterol.—Estimation of the cholesterol content of the α/β lipoprotein fractions of the serum was only made during the first two years of this investigation. Previous experience (Oliver and Boyd 1955) had shown that the oral administration of 200 μg. of ethinyl œstradiol to 55 hypercholesterolæmic men with coronary heart-disease reduced the α/β ratio from 9/91 to 15/85. During the two years while this ratio was measured, the average mean α/β ratio of the œstrogen group was 18/82 and that of the control group 10/90. Since electrophoretic estimation of the lipoproteins with subsequent elution of the cholesterol off the filterpaper is time-consuming, it was decided after two years to follow the changes in the serum lipids only by estimation of total serum-cholesterol and the C/P ratio.

Dose of Ethinyl Œstradiol

The starting dose of ethinyl œstradiol for all 50 men selected for the œstrogen group was 200 μg. daily, and this was taken in the form of one 100 μg. tablet twice daily. After one year of this dose, the mean serum-cholesterol of 13 men had fallen by less than 10%. Accordingly, the daily dose was increased to 250 μg. in 4 and to 300 μg. in 9 of these men. At the end of the second year, 5 of these 13 men still showed an unsatisfactory reduction in total serum-cholesterol and further increases up to 350 μg. daily were necessary. Despite this, the serum-cholesterol of 3 men was at no time more than 14% lower than their pretreatment values; none of these men had a further myocardial infarct during the five years' trial.

4 of the 50 men in the œstrogen group complained of extreme gynæcomastia and were permitted to reduce the dose to 150 μg. daily after two years. Although there was a slight rise in the serum-cholesterol and the C/P ratio of all 4 men, these values remained between 16% and 22% lower than their pretreatment levels; 2 died suddenly from myocardial infarction.

Feminising Effect

All except 2 of the 50 men in the œstrogen group developed gynæcomastia. This was well tolerated by the majority but 1 man developed a breast abscess and ethinyl œstradiol was discontinued. After the first six months of treatment, most of the men became accustomed to the presence of gynæcomastia and did not comment or complain about it. Other feminising effects are shown in table III. 4 men showed a growth of fine hair where they had previously been bald and 6 men needed to shave only twice a week.

TABLE III—FEMINISING EFFECTS OF ETHINYL ŒSTRADIOL IN 50 MEN

Gynæcomastia	96%
Depression of libido	74%
Loss of libido	46%
Decrease in beard growth	16%
Increase in hair growth	8%
Testicular pain	6%
Penile irritation	4%

TABLE IV—CAUSES OF DEATH, AND OF WITHDRAWAL FROM TRIAL, DURING 5-YEAR STUDY

—	Control group	Œstrogen group
Total number at start of trial	50	50
Total number at end of trial	32	28
Deaths:		
Myocardial infarct or sudden death	10	13
Cerebral vascular incident	0	2
Dissecting aortic aneurysm	0	1
Bronchial carcinoma	2	0
Pneumonia	0	1
Discontinued:		
Anticoagulant therapy after re-infarction	4	1
Cerebral vascular accident	0	1
Severe congestive heart-failure	0	1
Breast abscess	0	1
Uncooperative	2	1

TABLE V—NUMBER OF MEN WITH ONE OR MORE INCIDENTS OF MYOCARDIAL ISCHÆMIA AND INFARCTION

—	Control group	Œstrogen group
Total number of men at start of trial	50	50
Number of men with further acute incidents	24	22
Nature of acute incidents:		
Acute coronary insufficiency	6*	4
Non-fatal myocardial infarction	8‡	5†
Fatal myocardial infarction	10‖	13†§

* 1 man had two attacks.
† 1 man had previous acute coronary insufficiency.
‡ 2 men had two attacks.
§ 1 man had previous non-fatal myocardial infarction.
‖ 1 man had previous acute coronary insufficiency and previous non-fatal myocardial infarction.

Causes of Withdrawal from Trial

As can be seen from the figures at the foot of fig. 1, the number of men in both groups decreased during the five years of the trial. This was due not only to deaths but also to withdrawal of 11 of the 100 men (table IV). Included in these 11 are 5 men who had a further incident of myocardial ischæmia or infarction for which they were admitted to the care of other physicians who advised long-term anticoagulant therapy.

Causes of Death

In table IV the causes of death in the control and in the œstrogen group are listed.

Unfortunately, it has been possible to obtain necropsies on only 7 of the 23 patients who died at home; 3 of these were obtained on men in the control group and 4 on men in the œstrogen group. In each case, very precise assessment was made of the degree of coronary atheroma and of the coronary collateral circulation (according to the recommendations laid down in the World Health Organisation technical report no. 143, 1958). There was no unexpected or remarkable feature in the necropsies of those men who had received œstrogens. Of the 23 men who are presumed to have died from further myocardial infarction, 15 died suddenly at home or at their work. In each case the family doctor, the relations, or the workmates of the deceased men were interviewed, and as far as could be established death occurred from either sudden cardiac arrest, further myocardial infarction, or acute left ventricular failure.

Recurrence of Myocardial Ischæmia and Infarction

Second or third episodes of myocardial ischæmia or infarction occurred in 24 men in the control group and in 22 men in the œstrogen group. The details of these are listed in table V. From table VI it can be seen that these incidents were evenly distributed between the two groups throughout the five years of study. The survival-time in months was 2280 for the œstrogen group and 2289 for the control group. There were minor differences in the survival-time according to age but these were not statistically significant.

The number of further incidents of myocardial ischæmia or infarction was too small to allow any useful analysis by age, and from table VII there is no definite indication that age has operated in a different way in the two groups. There were proportionately fewer deaths in the control group between the ages of 55 and 64, but the difference is not statistically significant, and there was no other factor, such as the subsequent development of hypertension or angina, which could account for this difference.

Table VIII shows that there was no significant difference between the two groups in the number of subsequent incidents of myocardial ischæmia or infarction according to the site of the original myocardial infarct.

Table IX shows that there was no significant difference between the groups in the incidence of subsequent myocardial ischæmia or infarction according to the pre-treatment level of serum-cholesterol. Thus, there is nothing to indicate from this study that those with high-serum-cholesterol levels are likely to benefit most from their continued reduction.

Other Cardiac or Vascular Manifestations

A number of electrocardiographic abnormalities other than myocardial infarction developed in both groups (table X). There was, however, no significant difference in the distribution of these abnormalities between the two

TABLE VI—DISTRIBUTION OF ACUTE EPISODES OF MYOCARDIAL ISCHÆMIA AND INFARCTION

Time after starting œstrogen or inert tablets	Acute coronary insufficiency		Non-fatal myocardial Infarct		Fatal myocardial infarct	
	Control group	Œstrogen group	Control group	Œstrogen group	Control group	Œstrogen group
0–3 months	0	0	0	1	1	1
3–6 „	0	0	2	1	1	1
6–12 „	1	0	3§	0	1	1
1–2 years	2‖	3	0	2*	2	3
2–3 „	0	1	2	0	2	3*†
3–4 „	1	0	1	0	1	2
4–5 „	2	0	0	1	2‡	2
Number of incidents	6	4	8	6	10	13

* 1 man had previous acute coronary insufficiency.
† 1 man had previous non-fatal myocardial infarction.
‡ 1 man had previous acute coronary insufficiency and previous non-fatal myocardial infarction.
§ 1 man had subsequent non-fatal myocardial infarction.
‖ 1 man had subsequent acute coronary insufficiency.

TABLE VII—NUMBER OF MEN WITH ONE OR MORE INCIDENTS OF MYOCARDIAL ISCHÆMIA AND INFARCTION, ACCORDING TO AGE

Age in years	Control group				Œstrogen group			
	Total number of men	Acute coronary insufficiency	Non-fatal myocardial infarct	Fatal myocardial infarct	Total number of men	Acute coronary insufficiency	Non-fatal myocardial infarct	Fatal myocardial infarct
35–44	12	2	1	3	7	1	1†	1
45–54	20	2*	4*	5§	22	1	1	5
55–64	18	2	3*	2	21	2	3	7†‡

* 1 man had two attacks.
† 1 man had previous acute coronary insufficiency.
‡ 1 man had previous non-fatal myocardial infarction.
§ 1 man had previous acute coronary insufficiency and previous non-fatal myocardial infarction.

TABLE VIII—NUMBER OF MEN WITH ONE OR MORE ACUTE INCIDENTS OF MYOCARDIAL ISCHÆMIA AND INFARCTION, ACCORDING TO SITE OF FIRST MYOCARDIAL INFARCT

Site of first myocardial infarct	Control group				Œstrogen group			
	Total number of men	Acute coronary insufficiency	Non-fatal myocardial infarct	Fatal myocardial infarct	Total number of men	Acute coronary insufficiency	Non-fatal myocardial infarct	Fatal myocardial infarct
Anterior	19	0	4†	5‖	19	0	3	6
Posterior	19	4	2*	4	14	1	2‡	4§
Septal	4	0	0	1	9	2	0	3
High anterior or high posterior	8	2	2*	0	8	1	0	1

* 1 man had two attacks.
† 1 man had previous acute coronary insufficiency.
‡ 2 men had previous acute coronary insufficiency.
§ 1 man had previous non-fatal myocardial infarction.
‖ 1 man had previous acute coronary insufficiency and previous non-fatal myocardial infarction.

TABLE IX—NUMBER OF MEN WITH ONE OR MORE ACUTE INCIDENTS OF MYOCARDIAL ISCHÆMIA AND INFARCTION, ACCORDING TO PRETREATMENT LEVEL OF SERUM-CHOLESTEROL

Serum-cholesterol before treatment (mg. per 100 ml.)	Control group				Œstrogen group			
	Total number of men	Acute coronary insufficiency	Non-fatal myocardial infarct	Fatal myocardial infarct	Total number of men	Acute coronary insufficiency	Non-fatal myocardial infarct	Fatal myocardial infarct
More than 260	16	1	4*	3	17	3	1	5
Less than 260	34	5*	4*	7§	33	1	4†	8‡†

* 1 man had two attacks.
† 1 man had previous acute coronary insufficiency.
‡ 1 man had previous non-fatal infarction.
§ 1 man had previous acute coronary insufficiency and non-fatal myocardial infarction.

groups. Table XI lists a number of vascular complications other than myocardial ischæmia or infarction. Although rather more complications occurred in the œstrogen group, there is no significant difference in the distribution of any one of these between the two groups.

Coagulation Tests

Table XI shows that 5 men in the œstrogen group had a subsequent cerebral thrombosis and 5 developed thrombophlebitis of a leg vein; in contrast, there were only 3 such incidents in the control group. To investigate the possibility that œstrogens might have induced a thrombotic tendency, two studies were made of certain in-vitro coagulation tests during the administration of œstrogens.

During the fourth year of the trial, 12 men from each group were studied. In these men, the whole-blood clotting-time, silicone clotting-time, calcium clotting-time (using oxalated, citrated, or siliconed plasma), prothrombin-time, and 'Stypven' time were estimated in duplicate weekly for eight weeks. There was no significant difference between the groups.

Subsequently, these same in-vitro coagulation tests were studied in duplicate in 12 other men at weekly intervals for three weeks before œstrogen administration, for three weeks when the patients were receiving 1 mg. daily of ethinyl œstradiol, and for three weeks after œstrogen administration. There was no significant change in these tests as a result of this large dose of ethinyl œstradiol.

Œstrogen Withdrawal Effects

When ethinyl œstradiol was withdrawn after five years' continuous administration, there was an abrupt and striking rise in the serum-cholesterol which approximated within three weeks to that of the control group. The serum-cholesterol of the œstrogen group rose after three months to 272 ± 41 mg. per 100 ml., in contrast to 239 ± 39 mg. for the control group (fig. 1). A similar but smaller rebound was seen in the hypercholesterolæmic subgroup (fig. 2). This rebound, when the serum-cholesterol reaches levels higher than those before treatment, has also been observed after administration of thyroid hormones (Oliver and Boyd 1961).

When the œstrogen was stopped, the gynæcomastia gradually disappeared, but it was still present in half of the men six months later. Libido which had been depressed or lost returned within three or four weeks in the younger men but did not return in men over 55. Those who had developed hair where they had previously been bald became bald once more, and those whose beard growth had decreased had again to shave every day. A number of other men noted less beard growth while receiving ethinyl œstradiol and a return to usual growth after withdrawal of œstrogens.

After the œstrogen therapy was discontinued, there was a mean increase in weight of 6 lb. (range 0–13 lb.) during the first four months.

TABLE X—ELECTROCARDIOGRAPHIC ABNORMALITIES, OTHER THAN MYOCARDIAL INFARCTION, WHICH DEVELOPED DURING THE 5 YEARS

Electrocardiographic abnormality	Control group (no. of men)	Œstrogen group (no. of men)
Frequent ventricular extra-systoles or ventricular tachycardia	2	1
Partial heart-block	0	1
Left ventricular hypertrophy or strain	4	4
Partial left bundle-branch block	3	2
Complete left bundle-branch block	0	2
Complete right bundle-branch block	1	0

TABLE XI—VASCULAR COMPLICATIONS, OTHER THAN MYOCARDIAL ISCHÆMIA OR INFARCTION, WHICH DEVELOPED DURING THE 5 YEARS

Vascular complication	Control group (no. of men)	Œstrogen group (no. of men)
Severe effort angina (4 attacks daily)	3	4
Intermittent claudication	4	7
Cerebral thrombosis	1	5
Hypertension (diastolic blood-pressure over 100)	12	11
Congestive cardiac failure	5	7
Thrombophlebitis of leg veins	2	5*
Pulmonary infarction	2	2*

* 1 man had two attacks.

Discussion

This study in men who had survived their first myocardial infarction shows that administration of ethinyl

œstradiol can reduce the cholesterol, the cholesterol/phospholipid ratio, and the β-lipoproteins in the serum to accepted normal values, without any escape over a five-year period. Since previous studies have indicated that most œstrogens have the same effect on the serum lipids, this conclusion probably applies to all œstrogens.

The number of subsequent incidents of myocardial infarction or ischæmia, however, did not differ significantly in the œstrogen and control groups. Hence it seems that in men with coronary heart-disease, continued reduction of the serum lipids does not reduce the incidence of subsequent myocardial infarction.

There are three principal criticisms of this study. First, the small size of the group has precluded certain statistical cross-analyses; but this is to some extent compensated by the exclusion of many variables known to influence prognosis adversely and by the full and regular follow-up examinations undertaken by the same observer. Secondly, necropsies were obtained from only 7 of the 23 patients who died from myocardial infarction. Of these 23 men, 15 died suddenly at home or at work and the physician conducting the study was not informed early enough to obtain a necropsy; but, as far as could be established, further myocardial infarction or cardiac arrest was responsible for the patient's death. Thirdly, a potent œstrogen was used; all the men developed feminisation, and this cannot be regarded as a physiological means of reducing serum lipids in men.

In the œstrogen group, there were more thromboembolic episodes than in the control group. Though the numbers were not significantly different, this finding has caused us concern, since it could be argued that any benefit from lowering of the serum-cholesterol might be annulled by an increased thrombotic tendency. Yet it is probably unreasonable to couple incidents of arterial thrombosis (such as cerebral thrombosis) with incidents of venous thrombosis (such as thrombophlebitis of leg veins),

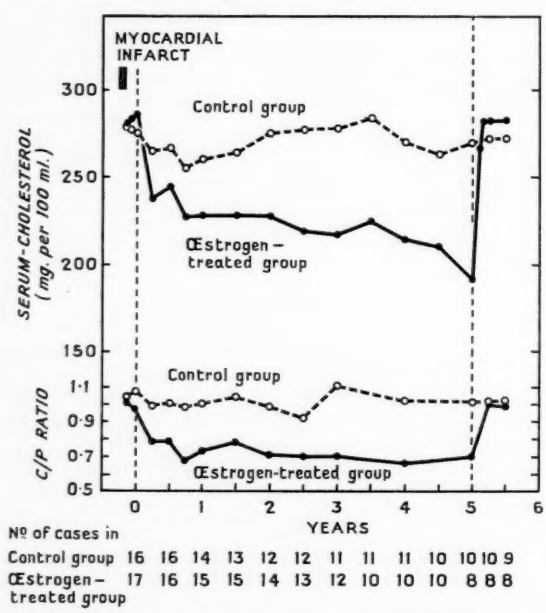

Fig. 2—Changes in the serum-cholesterol and C/P ratio during the 5-year study in 33 survivors of first myocardial infarction whose pretreatment level of serum-cholesterol was more than 270 mg. per 100 ml.

since the events leading to thrombus formation in the arterial system are probably dissimilar from those producing thrombosis in the venous system. Tests of coagulation in vitro showed no significant differences in the two groups; but such in-vitro tests of coagulation have, of course, a number of shortcomings, of which the chief is that they may not reflect any tendency to form intravascular thrombosis. Hence it cannot be said that we have definite evidence that the long-continued administration of œstrogens has not produced a thrombotic tendency.

In this connection, it should be mentioned that a conjugated œstrogen, premarin, has been used as a hæmostatic (Jacobson 1954, Menger 1955). Borchgrevink et al. (1960), however, did not find that premarin had a hæmostatic action and concluded that all clinical studies claiming a good hæmostatic effect lacked adequate control groups. Even if sound evidence that œstrogens are hæmostatic is later forthcoming, this will not necessarily mean that they increase the tendency to thrombosis. Moreover, there is no evidence that œstrogens induce hypercoagulability in men (Borchgrevink et al. 1960, Nilsson 1960), although Johnson (1957) has reported an increase in the concentration of prothrombin and factor v in dogs after large intravenous doses of premarin.

Another study of the effects of long-term administration of an œstrogen to men with coronary heart-disease has recently been reported in abstract (Stamler et al. 1960), a fuller report of the first three and a half years having been published previously (Stamler et al. 1959).

In this study the effect of the oral administration of premarin was evaluated in 276 men who had myocardial infarction under the age of 50. Placebo-treated and premarin-treated groups were divided into subgroups according to whether patients had a " good " or " poor " long-term prognosis. 165, of whom 97 were given premarin, were regarded as having a good long-term prognosis and are comparable to our patients. Despite sustained depression of the serum-cholesterol and C/P ratio, and elevation of α-lipoproteins, mortality-rates were similar in the groups treated with œstrogen and with placebo. Those regarded as having a poor long-term prognosis included patients whose acute myocardial infarct was complicated by shock or severe congestive failure and patients with more than one myocardial infarct. In these patients continued administration of premarin resulted in a suggestive, though inconclusive, improvement in mortality as compared with a comparable control group.

Recently, Marmorston et al. (1960) have reported that small doses of premarin, insufficient to induce any significant changes in the serum lipids, have after two years reduced the mortality-rate of men with myocardial infarction. Since these results contrast with those obtained with ethinyl œstradiol, they conclude that the benefit of premarin " may be mediated by constituents whose protective activity greatly exceeds their feminising potency ". These workers give insufficient clinical details about the selection of their patients and the comparability of their two groups. Nor is it stated whether factors which are known to influence the prognosis after myocardial infarction have been excluded or balanced between the two groups. Thus, it is not possible to make even a rough comparison between Marmorston's study and our own.

The results of our study, and those of Stamler et al. (1960) imply that reduction of the serum lipids in patients who have developed clinical features of coronary disease does not improve prognosis. This suggestion received support from Roe et al. (1960), who have studied the five-year mortality-rates of survivors from myocardial infarction in relation to their concentration of serum lipids, including analysis of standard S_f lipoprotein concentrations. The five-year survival-time was similar for each lipid fraction studied, and their results indicate that, once myocardial infarction has occurred, there is no relation

between survival and the concentrations of serum lipids. This is not altogether surprising, since the prognosis of patients with clinical manifestations of coronary disease may be far more closely related to a thrombotic tendency, to impaired myocardial efficiency, or to some other factors, than to hypercholesterolæmia. Nor would it be particularly surprising if further and more comprehensive studies show that reduction of the serum lipids does not improve the prognosis of patients once they have developed any of the clinical features of coronary heart-disease. There is no good correlation between serum-lipid levels during life and atherosclerosis at necropsy (Paterson et al. 1960). One only has to consider the extensive structural changes in the coronary arteries of such patients to wonder how reduction of the lipid level in the serum could make much difference at this stage in their disease. These patients may have one or many coronary occlusions, often with extensive destruction of the internal elastic lamina. Some arterial segments are stenosed and others dilated, and the media shows hyaline degeneration and often calcification.

For these reasons, it is probably unsound to test the value of cholesterol-lowering diets or drugs in patients with clinically manifest coronary heart-disease. To reach a definite conclusion as to whether the reduction of elevated serum lipids decreases the risk of developing myocardial infarction, long-term studies are most needed in apparently healthy people in whom disease of the coronary arteries is less advanced. Such studies would require the continued cooperation of a very large number of volunteers.

Summary

The subjects of this study were 100 survivors of a first myocardial infarction. They were selected from 186 patients with coronary heart-disease in order to obtain a homogeneous group. For five years, 50 of these men received a potent œstrogen and 50 were given lactose.

In the œstrogen group, significant reduction of the serum-cholesterol and the cholesterol/phospholipid ratio in the serum was evident throughout the five years of treatment. In the control group there was no significant change in the serum lipids.

The morbidity and mortality of the two groups did not differ significantly during the five years. 18 men in the œstrogen group and 18 men in the control group had further myocardial infarction. Analysis of morbidity and mortality according to age, the pretreatment level of serum-cholesterol, the site of the first myocardial infarct, the presence of obesity, and the subsequent development of hypertension, angina, and congestive heart-failure, showed no significant difference between the groups.

This study suggests that continued reduction of the serum lipids does not improve prognosis once myocardial infarction has occurred.

We would like to thank Dr. Rae Gilchrist for his advice and encouragement and for permission to study patients under his care; Dr. S. H. Davies for blood-coagulation studies; Mr. S. Sklaroff for statistical advice; and Mrs. F. Bird and Mrs. A. Gray for technical assistance. This research was supported by a grant from the Scottish Hospitals' Endowment Research Trust.

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STAPHYLOCOCCAL INFECTION OF OPERATION WOUNDS WITH SPECIAL REFERENCE TO TOPICAL ANTIBIOTIC PROPHYLAXIS

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DESPITE a determined effort by hospitals throughout the country to reduce the incidence of surgical wound infection, the problem remains largely unsolved. A recent report by the Public Health Laboratory Service (P.H.L.S.) (1960) puts the rate of frank wound sepsis in twenty-one hospitals undertaking general surgery within the range 4·7 to 21·8%, with an average of nearly 10%. Three-quarters of the infections were caused by *Staphylococcus aureus* alone or in combination with coliform bacteria.

The object of the present report is to submit data relating to staphylococcal infection of operation wounds in a busy general hospital over a period of four years, with emphasis on the part played in reducing the sepsis-rate by a multiple antibiotic spray (' Polybactrin ') containing neomycin, polymyxin B, and bacitracin.

Background to the Investigation

The frequency with which clean surgical wounds became infected with staphylococci in this hospital during 1955–56 caused considerable disquiet among the staff, and towards the end of 1956 a committee was formed with the object of checking and reducing the infection. Various precautionary measures were recommended by the committee: these included the use of vacuum cleaners and other dust-suppressive measures, the gradual replacement of woollen with cotton blankets, a general tightening-up in sterilisation procedures, and strict attention to theatre and ward hygiene, as well as minor recommendations too numerous to mention in detail.

During the next year the situation was carefully

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TABLE I—TYPE AND DURATION OF OPERATION (SEE TEXT)

Type of operation	No. of operations	No. of infections	Av. duration (mins.)	
			Cases	Controls
Abdominoperineal resection	34	6 (17·6%)	59	65·5
Prostatectomy	133	8 (6·0%)	85·4	68·6
Cholecystectomy	73	4 (5·5%)	50	41·7
Open reduction of fracture femur	134	7 (5·2%)	52	34
Cystectomy	63	3 (4·7%)	149·3	148·3
Herniotomy	280	10 (3·6%)	34·3	32·3
Mastectomy	84	3 (3·6%)	58·3	53·6
Gastrectomy	91	3 (3·3%)	103·6	97
Stripping of varicose veins	123	3 (2·4%)	104	45
Appendicectomy	411	3 (0·7%)	37	24·3
Totals	1426	50 (3·5%)	66	55·5

watched, and it became increasingly clear that the preventive measures in force were having little or no effect on the wound-infection rate, which persisted at the high level of 5–10%.

Pathogenic staphylococci were isolated repeatedly on settle plates exposed in the operating-theatres, wards, and corridors; and it was believed that many, if not most, of the wound infections were acquired at the time of operation from aerial or contact contamination. Although no patient died as a consequence of infection of his wound, there were a few deaths from staphylococcal pneumonia and enterocolitis in the hospital at this time, and a more direct and positive course of action seemed to be needed to reduce wound sepsis and thus to limit at least one source of cross-infection. To this end it was decided to recommend that the surgical staff should use prophylactically a pressurised powder spray of polybactrin, the preparation to be sprayed periodically into the wound during the course of the operation. By April, 1958, most of the surgeons were using this routinely in major surgery.

From Jan. 1, 1957, until Dec. 31, 1960, all wounds infected with *Staph. aureus* were recorded in a special register, together with a note of the patient's age, the nature and duration of the operation, and other relevant data. The figures given below are based on the contents of this register and on records kept in the operating-theatre.

Material and Methods

The hospital is a busy general and maternity hospital of 277 beds, with an average turnover-interval of 1·49 days, and an average stay per patient of 11·88 days. All major surgery is performed in two adjacent theatres between the acute surgical wards on the main surgical floor; the theatres are ventilated by means of a plenum plant (see later).

During the four-year period of the survey the wounds of 6419 major operations qualified for inclusion in the analysis. These were incisional wounds, measuring 3 in. or more in length, for operations which lasted for at least fifteen minutes. The great majority of wounds were for clean elective surgery, but emergency operations were also included provided the site and nature were such that infections of the wounds with *Staph. aureus* would not normally occur—e.g., appendicectomy for early acute appendicitis, pinning of fracture of neck of femur, &c. Excluded from the analysis were all minor operations, operations on the eye, ear, nose, and throat, and on the anal region (except when combined with anterior resection of rectum), and those on sites known to be infected with staphylococci—e.g., some operations on the urinary tract in the presence of a staphylococcal urinary infection.

A swab was sent to the laboratory as soon as a wound was seen to be, or suspected to be, infected, as judged by the presence of purulent discharge or at least obvious inflammation; this was usually seen at the time of the first dressing. Swabs were not taken if the wound appeared to be healing satisfactorily. All swabs were cultered on blood-agar plates and if *Staph. aureus* (coagulase-positive) was isolated, the case was entered as a wound infection in the register. The great majority of positive swabs yielded a heavy pure growth of *Staph. aureus*, but sometimes coliform bacteria and other pathogens were isolated along with the staphylococci. All strains of *Staph. aureus* were tested for sensitivity to eight antibiotics, and a small number were phage-typed.

Results

The figure shows the general incidence of infection for the series. Out of 6419 wounds 213 (3·3%) were infected with *Staph. aureus*, the infection in all cases being observed clinically and confirmed bacteriologically. There were 93 (6·7%) infections during the first year of the investigation, and the number thereafter fell progressively to 53 (3·2%) in 1958, 37 (2·2%) in 1959, and 30 (1·8%) in 1960. The frequency of wound infection decreased each year despite added pressure of work in wards and theatres due to increase in the number of operations.

Types of operation.—Table I shows the type of operation that led to a wound infection on three or more occasions between mid-1958 and the end of 1959. It will be seen that the sepsis-rate for abdominoperineal resection of rectum was much higher than that for any other operation; this was doubtless related to the extent and site of the operation, and to the fact that two wounds doubled the chance of infection. The infection-rate following operations on the gallbladder, although high (5·5%), was considerably less than that observed in the P.H.L.S. survey (14·9%). Prostatectomy and open reduction of fractured neck of femur also carried high rates of post-operative sepsis; the site of these operations, and also the advanced age of most of the patients, were probably contributing factors. Of the commonly performed operations, appendicectomy had the lowest infection-rate (0·7%).

Duration of operation.—The average length of the 50 operations which became infected was sixty-six minutes, and the operation lasted more than an hour on twenty-four occasions. For comparison 50 non-infected operations of the same type

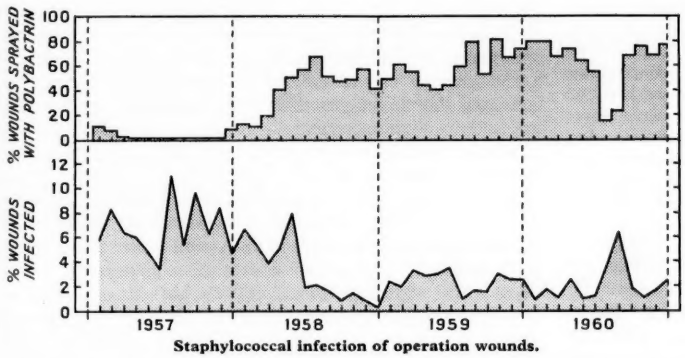
TABLE II—BACTERIA ISOLATED FROM 200 INFECTED WOUNDS

Organism	No. of wounds infected
Staph. aureus	172
" " + *Esch. coli*	26
" " + *Proteus mirabilis*	9
" " + *Streptococcus pyogenes*	6
" " + *Pseudomonas pyocyanea*	1

TABLE III—INCIDENCE OF INFECTION IN RELATION TO POLYBACTRIN

Period	No. of operations	Polybactrin	No. of infections	Sepsis-rate (%)	Difference	
					Observed	S.E.
January, 1957–December, 1960	3702	–	160	4·3	2·3	0·43
	2717	+	53	2·0		
January–December, 1957	1396	–*	93	6·7	4·3	0·70
January, 1958–December, 1960	5023	+†	120	2·4		
January, 1958–December, 1960	2338	–	69	3·0	1·1	0·44
	2685	+	51	1·9		
February, 1957–June, 1959	486‡	–	18	3·7	1·9	1·07
July, 1959–July, 1960	437‡	+	8	1·8		

*Polybactrin used in 2% of operations.
†Polybactrin used in 53% of operations.
‡Operations performed by one surgeon.



Staphylococcal infection of operation wounds.

and in the same proportion were chosen haphazardly from the operation registers for the same period. These operations lasted on average fifty-five minutes, and 16 were of an hour or longer.

Age.—The average age of 200 infected patients was 61·2 years; that of 200 non-infected major operations (taken consecutively from the first quarter of the 1959 operation register) was 52·0 years. The difference in age was not statistically significant, but 61% of infected as against 40% of non-infected patients were over the age of 60.

Sex.—Of the 200 infected patients 123 were male and 77 female; of the controls 111 were male and 89 female. The preponderance of male patients in both the infected and control groups is to be expected because most of the gynæcological surgery was performed at another hospital.

Season.—The sepsis-rate did not vary significantly in relation to the months or seasons of the year.

Bacteriology.—*Staph. aureus* was recovered in pure culture from 86% of the infected wounds. In the remaining cases it was accompanied by other pathogens, usually *Escherichia coli* (table II). The infecting staphylococci showed wide variation in their bacteriophage pattern. Among the first batch of twelve strains to be tested by the P.H.L.S., seven were found to belong to different types within groups I and III, and it was therefore decided to forego typing as a routine.

Sensitivity.—There was considerable variation in the sensitivity reactions of *Staph. aureus* to eight antibiotics:

Antibiotic	*% sensitive*
Penicillin	16
Tetracyclines	35
Streptomycin	50
Erythromycin	86
Chloramphenicol	88
Novobiocin	100
'Polybactrin' (10 strains tested)	100

The majority of strains were resistant to penicillin and tetracyclines, half were resistant to streptomycin, and a few were resistant to erythromycin and chloramphenicol; all strains were sensitive to novobiocin. Sensitivity tests were also carried out against polybactrin, using the technique devised by Turk (1959); of 10 strains tested from patients who had received the spray, all were found to be sensitive to the mixture, and separately to neomycin, and to a lesser extent bacitracin.

Polybactrin

From the figure it will be seen that, during 1957 and early 1958, when the spray was used on very few patients, the sepsis rate ranged from 3·3 to 11·1%. This was followed by a decline in sepsis which coincided with increasing use of the spray, and during this second phase the infection-rates were within the range 0 to 3·3%. The sudden increase in the incidence of sepsis during July and August, 1960, was the result of an experiment to confirm that the improvement was due largely, if not entirely, to the spray. All surgeons were asked not to use the spray except when absolutely necessary for a period of two months. The infection-rate for the previous six months had been 0·5–2%; by the end of the experiment it had risen steeply to over 6%. When spraying was reintroduced the rate dropped equally steeply to the pre-experiment level. During the two-month period the number of infections was the same as during the remaining ten months of the year—namely, 15.

It will be seen from table III that the overall sepsis-rate of wounds sprayed with the antibiotic combination was 2·0%, while that of the unsprayed wounds was 4·3%—a difference which is highly significant statistically (S.E. of difference—0·43). An equally significant difference was obtained when the incidence for the pre-polybactrin period (1957) was compared with that during 1958-60 when the spray was applied to over half the major operation wounds, the observed difference in this instance being 4·3% (S.E. of difference = 0·70). When comparison was made between almost equal numbers of sprayed and unsprayed wounds during 1958–60, the difference was less striking, but still significantly favourable to polybactrin (1·1%; S.E. of difference = 0·44).

One of the surgeons was somewhat sceptical of the value of this prophylactic measure, and until July, 1959, he refused to use it. He was persuaded to spray his wounds from this time onwards to provide comparable figures for operations performed by one surgeon. This surgeon's infection-rate before using the spray was 3·7%, and when he used the spray the rate dropped to 1·8%. This difference is not statistically significant, but it is noteworthy that the infection-rate for operations performed by this surgeon, already below the national average, was reduced by half.

TABLE IV—YEARLY INCIDENCE OF INFECTION IN RELATION TO POLYBACTRIN

Year	No. of operations	Polybactrin	Infections
1957	1364	−	91 (*6·7%*)
	32	+	2 (*6·3%*)
1958	968	−	37 (*3·8%*)
	693	+	16 (*2·3%*)
1959	709	−	14 (*1·9%*)
	974	+	23 (*2·4%*)
1960	661	−	18 (*2·7%*)
	1018	+	12 (*1·2%*)

The general trend throughout the full period as seen in the figure was for the rate of infection to be in inverse ratio to the amount of spray used, but one or two anomalies were noted:

When one examines the figures for each year that polybactrin was used (table IV), one finds that sprayed wounds were infected less often during 1957, 1958, and 1960, whereas in 1959 the infection-rate was 0·4% higher among wounds sprayed than among non-sprayed wounds. This coincided with a slight rise in the incidence of infection during the first half of 1959 when, according to the records, the spray was being applied to about half the wounds. This might be explained on the grounds that some of the surgeons, lulled into a sense of false security by the almost complete absence of infection during the preceding months, often applied the spray half-heartedly, and then only as an afterthought at the very end of the operation. When they were reminded that the spray should be applied at all tissue layers the infection-rate returned to its former low level.

Another anomalous finding was the near absence of infection among unsprayed as well as sprayed wounds at various times, but especially towards the end of 1958. This was

probably because the infection-rate for surgical patients throughout the hospital as a whole had been strikingly reduced, and there was therefore a corresponding reduction in the total number of hospital staphylococci available to contaminate other wounds. Moreover, when the spray was used at one operation or session some was likely to have been carried over in the atmosphere to the next. In short, all patients undergoing operation benefited from the use of the spray, but presumably the protection afforded was greater when the spray was applied directly into the wound under pressure. Conversely, a number of wounds became infected despite proper spraying with polybactrin, and the most likely explanation is that these later became infected in the ward, when the protective effect of the spray had worn off.

All but a few of the infections in clean surgical wounds were caused by *Staph. aureus*, and records were kept only of wounds infected with this organism. But the incidence of infection of wounds, both clean and " dirty ", with coliform bacilli was also greatly reduced while the spray was in use, no doubt because of the presence of neomycin and polymyxin in the antibiotic combination. Thus when polybactrin was not in use or used only very occasionally (January, 1957–March, 1958, and July and August, 1960) coliform bacilli were isolated in mixed culture with *Staph. aureus* twenty-nine times; during the much longer period when polybactrin was often used coliforms were isolated along with *Staph. aureus* only seven times.

During the early part of this investigation while operation-wound infection was high, minor staphylococcal infection in the form of boils, " septic spots ", &c., were common among patients of all ages in medical and maternity, as well as surgical, wards, and also among the nurses. Records were kept of nurses who reported sick with surface staphylococcal infection; the incidence of this type of infection fell throughout the four years, the number infected for each year from 1957 being 72, 33, 23, and 22 respectively.

Discussion

The practice of using antibiotics routinely for prophylaxis against infection in clean general surgery has been deprecated by many, including Howe (1957), Linder (1957), and Barnes et al. (1959), all of whom have reported increased rates of postoperative staphylococcal infection in patients so treated. These reports refer to surgical patients given, for the most part, prophylactic penicillin and streptomycin by the systemic route—a procedure which is known to carry certain risks, of which toxic reactions, superinfection with antibiotic-resistant bacteria, and the propagation of resistant strains are the most serious. We were aware of these objections when we embarked on our prophylaxis programme, and we have watched closely for any untoward effect, but so far none of these disadvantages has applied in the case of polybactrin. The fact that the three antibiotics (neomycin, polymyxin B, and bacitracin) incorporated in the spray are not normally given systematically has helped; in applying this preparation directly to wounds one is simply introducing a potent but non-irritant antiseptic powder.

Throughout the whole of this investigation no case of allergy or other side-effect has arisen among thousands of patients who have received the spray or among members of the theatre-staff who have been in daily contact with the antibiotic. Nor, as far as is known, has there been any superinfection—a fact which one would attribute to the mixture of antibiotics whose combined antibacterial action covers nearly all pathogenic bacteria, both gram-positive and gram-negative. Moreover, under laboratory conditions, Turk (1959) has demonstrated synergism between neomycin and bacitracin, and between bacitracin and polymyxin in respect of *Staph. aureus*; and it may be assumed that so long as this triad of antibiotics is applied topically in high bactericidal concentration resistant mutations are unlikely to emerge. In the case of *Staph. aureus* which is sensitive to two of the three antibiotics, the chance of any one strain being or becoming simultaneously resistant to both neomycin and bacitracin must be very remote. Lowbury (1960) tested over 300 strains and could not demonstrate resistance to either of the two antibiotics, although strains of *Staph. aureus* resistant separately to neomycin and bacitracin have been reported recently from America (Quie et al. 1960).

Polybactrin has already been used to good effect in the prevention of operation-wound infection in both theatre and ward. For example, Gibson (1958) used the spray in the theatre during 250 neurosurgical operations, and by this means restricted the incidence of major sepsis to 0·4% while the infection-rate in a comparable series of unsprayed cases was 7·2%. Gillespie et al. (1959) sprayed open and drained wounds in surgical wards to prevent staphylococcal cross-infection, and reduced the sepsis-rate from 18·7% to 13·5%.

Despite one or two anomalous findings the present study offers fairly convincing evidence that the decline in wound infection was due largely to the use of polybactrin as a prophylactic. We have looked for and failed to find any other factor which might have had an appreciable effect on the infection-rate. For example, one might argue that the patients were being infected by the nurses in 1957, and that the improved sepsis-rate since 1958 is simply a reflection of reduced infection among the nursing-staff. But the records show this to be unlikely; for the resurgence of wound infection during July and August, 1960, while the " ban " on polybactrin was in force, was not preceded or accompanied by a rise in staphylococcal infection among the nurses.

The ventilation system in the theatre suite was modified during the course of the investigation, and this too must be considered as a possible contributing factor to the decline of infection:

At the beginning of the investigation ventilation, which was by means of a plenum plant with an oil-covered air filter, was found to be unsatisfactory because the pressure of air in the theatre was less than that outside it. Thus a slight negative pressure prevailed for most of the time, and simple tests showed that contaminated air from the corridors was filtering under the doors and entering the theatres. Steps were taken to reverse the direction of air-flow by increasing the pressure of the plenum plant, but the advantage of delivering cleaner air to the theatres was offset by the distraction of the noise of the fan and the creation of cold draughts, especially in the winter months. Consequently full plenum ventilation was used very intermittently, and then only from January, 1959, by which time the infection-rate was already at a minimum. The rate did in fact rise immediately after the installation of the new ventilation plant; but, as already mentioned, it was thought that this was due more to incorrect use of the spray than to a change in ventilation technique.

The only other major change during the whole period of the investigation concerns the sterilisation unit:

Certain structural adjustments were made to the autoclaves in late 1957 and early 1958 to increase their efficiency, and although sterility tests did in fact suggest some improvement, it was at least six months before the infection-rate showed signs of abating, by which time the spray was being used in increasing quantities.

The crucial test was in the summer of 1960, when spraying with polybactrin was deliberately withheld. During this period there was no other deviation from routine, and the steep rise in the infection-rate during the " ban " and its return to a low level when spraying was resumed is strong presumptive evidence that factors other than the spray had little influence on the incidence of infection.

Although a case can be made out for the routine use of topical antibiotics as a sepsis-prophylactic during major surgery, it is not suggested that this procedure should in any way supplant the strict observance of the principles of asepsis. Rather should the technique be used as an ancillary to established aseptic disciplines. According to Williams (1959), " there is no one way in which staphylococci spread in a hospital and there is no one prophylactic method by which spread can be prevented ". Operation wounds are thought to become infected from one of three sources—aerial and contact infection in the threatre, cross-infection in the wards, or autoinfection with the patient's own staphylococci. It may be difficult to determine which source is responsible for infections in any one hospital, and indeed all three may play a part from time to time. In the final analysis, however, the causative factor in wound infection is the implantation of staphylococci in the operation wound itself, and when conditions suggest that the majority of infections take origin in the theatre, the routine use of a topical antibiotic spray seems to be a justifiable preventive measure. This manœuvre not only provides some protection to the individual patient but, by reducing the infection-rate as a whole, also helps to confine the total load of staphylococci in the hospital environment to manageable proportions.

Summary

Staphylococcal infection of surgical wounds was studied in one hospital for four years. The yearly infection-rate fell progressively from 6·7% in 1957 to 1·8% in 1960. Reasons are given for the belief that the improvement was due to the increasing use in the operating-theatres of an antibiotic mixture of neomycin, bacitracin, and polymyxin B (' Polybactrin ') which was sprayed periodically into the wound during the course of the operation.

The incidence of infection among wounds which were sprayed in this way (2·0%) was less than half that of wounds not so treated (4·3%), and during the last year of the survey the infection-rate among over 1000 sprayed wounds was as low as 1·2%.

Operations which were followed by wound infection took on average ten and a half minutes longer to perform than those that remained healthy, and infected patients were on average 9 years older than patients with comparable operations whose wounds healed without sepsis.

While undertaking this investigation and preparing the report I have received the willing help and cooperation of many people in many ways. I thank them all, and regret that they are too numerous to mention by name.

' Polybactrin ' is manufactured by Calmic Ltd., Crewe, Cheshire.

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ESSENTIAL HYPERTENSION AND INHERITANCE OF VASCULAR REACTIVITY

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IN severe hypertension in man, pressor stimuli induce greater constriction of blood-vessels than the same stimuli in normotensive individuals (Duff 1957, Mendlowitz et al. 1957, Moulton et al. 1958, Doyle et al. 1959). While the difference in response is exaggerated by the difference in the initial state of constriction of the vessels, the heightened vascular reactivity in hypertension is not solely due to this, but represents a true enhancement of the effects of pressor stimulation (Doyle et al. 1959). This exaggerated response to constrictor stimulation might precede the high blood-pressure, or be a consequence of it. If it precedes the development of high pressure, it might be found more frequently in the children of hypertensive people than in the children of people with normal blood-pressure.

We report here a comparison of the response of the forearm circulation to locally infused noradrenaline in sons of patients with high blood-pressure, with the response of a group of young men whose parents had normal blood-pressures.

Methods

Selection of Subjects

Patients attending the hypertensive clinics at the Royal Melbourne Hospital and at the Alfred Hospital, Melbourne, were questioned as to their familial incidence of high blood-pressure. These patients had been extensively investigated to exclude possible causes of secondary hypertension, and all were thought to have severe essential hypertension. The adult sons aged 21–35 of those who had an unequivocal strong family history of high blood-pressure were asked to volunteer for investigation. The blood-pressure of the other parent was not usually known.

A group of medical students and young physicians served as controls, and measured the casual blood-pressures of their parents at home. If both of their parents' casual blood-pressures were below 160/100 mg. Hg, they were accepted for the control group. 26 sons of patients with essential hypertension and 25 sons of people with casual blood-pressure below 160/100 were studied.

Technique

This was identical with that previously reported (Doyle et al. 1959), consisting of the infusion of 0·4 μg. per min. and 0·2 μg. per min. of noradrenaline into the left brachial artery. Forearm blood-flow in both arms was measured with mercury in rubber strain gauges (Whitney 1949). The effects of the infusion of noradrenaline were measured by comparing the blood-flow during the infusion of saline and expressing each as a ratio of the flow at the corresponding time in the opposite arm. The results are expressed as the per cent. fall in blood-flow induced by noradrenaline.

Blood-pressure was measured by auscultation before and after the procedure was begun.

Results

The hypertensives' sons had a significantly greater mean age than the normotensives' sons, the difference being 3·8 years. The systolic and diastolic blood-pressures were slightly higher in the hypertensives' sons, but the

TABLE I—HÆMODYNAMIC DATA

—	Normotensives' sons	Hypertensives' sons	Significance of difference
Age (yr):			
Mean	22·9	26·7	$P<0.001$
Range	21–31	21–36	
S.D.	±2·32	±4·83	
Systolic blood-pressure (mm. Hg):			
Mean	129·2	136·0	$0.1>P>0.05$
Range	95–150	110–160	
S.D.	±15·33	±13·53	
Diastolic blood-pressure (mm. Hg):			
Mean	78·2	81·1	$P>0.2$
Range	65–95	65–100	
S.D.	±8·82	±7·54	
Forearm blood-flow (ml/. 100 ml./min.): •			
Mean	2·3	2·73	$P>0.2$
Range	1·3–7·4	1·2–6·3	
S.D.	±1·26	±1·33	
Forearm vascular resistance: †			
Mean	48	42	$P>0.2$
Range	15–75	13–87	
S.D.	±14·53	±18·22	
% fall in blood-flow due to noradrenaline:			
0·4 μg per min.			
Mean	46·9	58·6	$0.05>P>0.02$
Range	0–71	7–78	
S.D.	17·2	18·9	
0·2 μg. per min.			
Mean	35·7	45·0	$0.05>P>0.02$
Range	0–54	9–68	
S.D.	14·4	13·5	

• Before infusion. † Resistance = mean arterial pressure (mm. Hg) divided by forearm blood-flow (ml./100 ml./min.) in arbitrary units.

TABLE II—EFFECTS OF INFUSION ON NORADRENALINE

Subjects	Age (yr.)	Blood-pressure (mm. Hg)		Initial forearm blood-flow (ml./100 ml./min.)	% fall in flow due to noradrenaline	
		Systolic	Diastolic		0·4 μg. per min.	0·2 μg. per min.
Normotensives' sons:						
1	22	95	65	2·6	64	15
2	23	150	95	3·9	55	46
3	23	120	70	2·2	59	39
4	24	135	85	2·1	35	3
5	23	115	75	2·3	63	—
6	21	130	70	1·8	29	30
7	23	100	70	1·9	65	44
8	23	125	80	1·5	46	35
9	22	110	75	2·0	58	54
10	21	135	90	1·5	42	26
11	22	110	80	1·4	60	45
12	21	130	70	1·6	47	—
13	24	145	70	2·2	55	49
14	22	145	85	1·9	71	51
15	24	125	70	1·8	42	39
16	31	140	90	3·5	66	41
17	28	130	85	1·7	47	35
18	23	135	80	2·0	0	0
19	21	150	90	7·4	16	39
20	24	125	70	1·6	51	46
21	21	130	70	1·3	48	46
22	22	120	70	3·0	53	44
23	22	140	90	2·0	25	31
24	21	150	80	1·6	43	38
25	22	140	80	2·3	32	25
Hypertensives' sons:						
1	27	160	80	5·6	74	63
2	21	130	90	2·6	48	35
3	32	160	100	2·9	69	51
4	30	135	85	1·7	35	31
5	23	130	85	1·6	57	41
6	25	140	90	3·6	11	9
7	24	140	75	1·5	60	50
8	35	110	85	2·6	73	56
9	30	140	90	4·6	65	37
10	22	130	80	1·2	46	41
11	21	140	70	2·9	72	51
12	21	150	80	6·3	65	51
13	22	150	75	2·6	60	46
14	24	145	80	2·6	63	32
15	23	145	80	1·3	65	39
16	21	120	80	2·7	35	39
17	30	130	75	4·7	70	52
18	32	140	85	3·1	7	22
19	34	120	75	2·2	70	68
20	25	110	65	2·1	73	63
21	25	115	75	1·9	76	56
22	24	140	90	1·3	57	50
23	32	140	80	1·9	60	58
24	27	140	85	3·1	78	36
25	36	130	75	2·5	61	45
26	28	145	80	1·9	73	48

differences were not of statistical significance. The higher blood-pressures of the hypertensives' sons were offset by their slightly higher forearm blood-flow, so that the mean forearm resistance was a little higher in the normotensives' sons than in the hypertensives' sons. Thus the hæmodynamic situation in the forearms of the two groups was essentially identical (table I).

The effects of the infusion of noradrenaline are shown for the individuals in table II, and the distribution of the responses is shown in the accompanying figure. With both dose levels, the mean responses of the hypertensives' sons were significantly greater than those of the normotensives' sons. There is a substantial overlap of response between the two groups (see figure), but the proportion with large responses was greater in the hypertensives' sons than in the normotensives' sons.

TABLE III—PRESENT RESULTS COMPARED WITH THOSE PREVIOUSLY REPORTED FOR OLDER, AGED-MATCHED NORMOTENSIVES AND HYPERTENSIVES

Subjects	Mean age (yr.)	Mean response to noradrenaline 0·4 μg. per min.
Normotensives •	49·1 S.D. ± 10·8	48·0 S.D. ± 13·3
Normotensives' sons ..	22·9 S.D. ± 2·3	46·8 S.D. ± 16·8
Hypertensives' sons ..	26·7 S.D. ± 4·7	58·6 S.D. ± 15·5
Hypertensives •	48·0 S.D. ± 10·0	61·0 S.D. ± 8·6

• These results were published previously (Doyle et al. 1959).

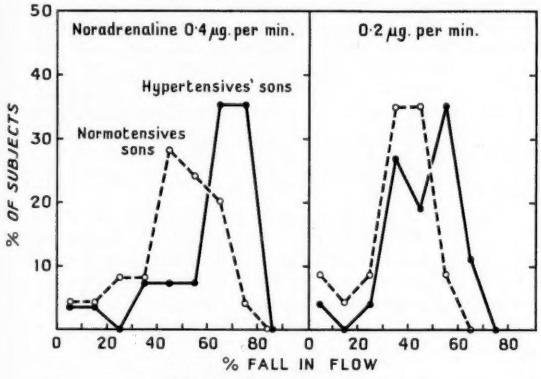
A comparison of the results obtained in the present study and of the results previously found by the same technique in groups of older, age-matched, hypertensive and normal subjects is shown in table III. The present series of normotensives' sons, although about 26 years younger than the normotensives previously studied, had a mean response almost identical with the older normotensives. The responses of the hypertensives' sons were thus greater than those of their contemporaries with normotensive parents, and also greater than those of their elders whose blood-pressure remained normal a generation later.

Discussion

In this investigation only the sensitivity to noradrenaline was studied, but in previous investigations it was found that hypertensive patients had a heightened vascular response to angiotensin and 5-hydroxy-tryptamine (Doyle et al. 1959) and a heightened pressor sensitivity to a synthetic pressor substance, s-methyl isothiourea (Doyle and Black 1955). Thus it is probable that people with essential hypertension have a heightened vascular reactivity to a variety of constrictor stimuli, rather than specifically to noradrenaline.

The mechanism responsible for the enhancement of vascular sensitivity to constrictor agents is obscure. In hypertension there is probably an anomaly of arterial smooth-muscle contraction—possibly a discrete entity dependent on a specific enzyme defect. It may be biochemical, and concerned with the degradation of locally released noradrenaline or with some other process involved in arterial muscular contraction, or it may operate through some structural aspect of smooth muscle.

Our present finding, that the sons of hypertensive patients have a greater vascular response to noradrenaline demonstrable at an age when their casual blood-pressures are normal, indicates that heightened vascular sensitivity is an inherited characteristic. We have little information about the mode of inheritance of this characteristic. The fact that only one parent was known to be hypertensive



Distribution of responses.

Figures derived from observations on 26 hypertensives' sons and 24 normotensives' sons for the 0·4 μg. per min. dosage, and on 26 hypertensives' sons and 23 normotensives' sons for the 0·2 μg. per min. dosage.

might be taken as evidence that heightened vascular sensitivity is inherited as a mendelian dominant character. If this is so the possibility that heightened vascular sensitivity is a specific defect would be strengthened.

The inheritance of increased vascular reactivity would obviously influence the likelihood of an individual becoming hypertensive, but probably it would be only one of many factors concerned in the pathogenesis of essential hypertension. The response of the individual to pressor stimuli must be at least as important as the magnitude and frequency of pressor stimulation in initiating or maintaining hypertension. Such a situation might explain at least partly the well-known familial incidence of essential hypertension (Platt 1947).

The observation that a heightened vascular response to constrictor drugs is present in this group of young men with hypertensive parents does not necessarily imply that the increased vascular response previously demonstrated in human hypertension is solely an inherited characteristic. It may be further reinforced by changes induced by, or accompanying, the development of the high blood-pressure itself. Similar changes in vascular sensitivity can be induced in laboratory animals by manœuvres which lead to high blood-pressure (McQueen 1956). However, the similarity of the mean response of these normotensive young men with hypertensive parents to the response obtained in established hypertension (table III) must imply that much of the heightened vascular reactivity in established hypertension is genetically determined.

Summary

Young adult normotensive sons of hypertensive parents were found to have a significantly greater vascular response to noradrenaline than young men of a similar age whose parents had normal blood-pressures.

Heightened vascular reactivity may depend on a specific defect, which is inherited as a dominant characteristic, and which is concerned, together with other factors, in the pathogenesis of essential hypertension.

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References at foot of next column

PERIODIC PARALYSIS WITH RESPONSE TO SPIRONOLACTONE

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PERIODIC paralysis not due to renal disease or adrenal tumour includes at least three distinct genetically determined diseases: classical periodic paralysis, adynamia episodica hereditaria (Gamstorp et al. 1956), and sodium-responsive normokalæmic periodic paralysis (Poskanzer and Kerr 1961). This study, like most that have been published, concerns classical periodic paralysis—the least rare of the three. Established features of the classical type include hypokalæmia during the attacks, rapid response to administered potassium salts, and precipitation of attacks by several manœuvres which lower serum-potassium—i.e., rest after exercise, carbohydrate feeding, and injection of insulin or adrenaline (see McArdle 1956, and Grob et al. 1957, for review of literature). More recently a few metabolic studies have shown that sodium retention may precede the attacks, and that paralysis can be induced by giving sodium salts and prevented by low-sodium diet or sodium depletion with the aid of diuretics (Conn et al. 1957, Rowley and Kliman 1960).

The association of sodium retention and hypokalæmia with periodic paralysis reveals a superficial similarity to primary hyperaldosteronism, and this has led to investigation of urinary aldosterone excretion in classical periodic paralysis. Conn et al. (1957) noted a rise in aldosterone excretion during the attacks, and postulated in intermittent hyperaldosteronism. Rowley and Kliman (1960) and Jones et al. (1959) did not find this association to be constant, and they concluded that aldosteronism, if present, was secondary.

The possible association of hypersecretion of aldosterone and attacks of weakness in classical periodic paralysis prompted us to try an aldosterone inhibitor in a patient with a severe form of the disease.

Case-report

A 40-year-old grocery warehouseman has had episodes of quadriplegia since the age of 16. These attacks occur about once a month, often after a heavy meal or on the day following heavy exertion, and they are usually present when he awakens in the morning. Each attack lasts about three days, gradually clearing. Meanwhile the patient is often completely paralysed though the use of facial muscles, chewing, swallowing, breathing, bladder control, and bowel function are retained. Profuse sweating is present and a sense of depression accompanies the attacks.

Weakness was precipitated in hospital by a high-carbohydrate meal, and by the injection of adrenaline or insulin. In each attack the serum-potassium was reduced, and on electromyo-

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graphic study the paralysed muscles showed an absence of electrical activity—the typical " cadaveric " response. Blood-pressure, urine analysis, blood-urea, and aminoacid excretion are normal. Serum electrolytes are normal between attacks. The patient is therefore regarded as having classical periodic paralysis.

A limited family history failed to reveal other cases of similar illness.

Previous Treatment

Two years after the episodes started it was discovered that potassium chloride taken by mouth after the onset would modify an attack of paralysis, though the medication was distasteful and only partially effective, and often caused diarrhoea. Various unsuccessful regimens were tried, including a diabetic diet, acetylcholine derivatives, and prostigmine. A low-starch diet seemed to reduce the frequency of attacks.

For the past ten years the patient has had a residual weakness between episodes of paralysis, despite regular dosage with potassium chloride. This weakness was interpreted as the permanent muscle change which has been described in long-standing cases by Bickerstaff (1953) and others. In the past year or two persistent general weakness had made it difficult for him to continue his work, and he asked for further help.

Studies in Hospital

The patient was admitted to the Royal Victoria Infirmary and observed in the ward for six weeks. Dietary intake was controlled, and the urinary output of sodium and potassium was measured in twenty-four hour aliquots; fæcal losses were studied only for a short period. Muscle strength was assessed regularly by his ability to pull out a spring balance, his facility in rising from the squatting position, and his performance on stairs. On a normal diet with potassium-chloride supplements of 4 g. three times daily there was improvement in muscle strength, but it remained below normal for a man of his size. Climbing stairs was a considerable effort. The effect of each dose of potassium chloride lasted only a few hours.

Withdrawal of potassium supplements and the administration of sodium chloride 10 g. precipitated a severe attack of paralysis, which resolved during four days while potassium-chloride supplements were reintroduced. A low-sodium diet (22 mEq. per day) without potassium supplements failed to produce any improvement on the patient's state before hospital admission. The same low-sodium diet with potassium chloride 4 g. three times per day gave no better response than the same supplements with a normal diet. The very low-sodium diet (8 mEq. per day) recommended by Conn et al. (1957) proved impracticable even in hospital and was out of the question as a long-term therapeutic measure.

Treatment with Spironolactone

Spironolactone, a specific antagonist of aldosterone and clearly related substances, was given in two separate courses for ten and nine days respectively. A dose of 200 mg. twice a day was used during the first course. The dose was reduced to 100 mg. twice a day during the second course with no loss of therapeutic effect. Sodium intake was 22 mEq. per day during the first course, and 35 mEq. per day during the second. On both occasions there was a striking improvement in muscle strength, maintained throughout the day and greatest within twenty-four hours of starting therapy. The patient could now mount stairs two at a time without tiring, and the performance of other muscle groups was proportionately improved. A heavy carbohydrate meal during spironolactone therapy did not produce paralysis. Replacement of spironolactone with a placebo was accompanied by subjective complaint and objective deterioration.

Maintenance therapy with spironolactone 100 mg. twice daily for the last eight months has been associated with increased muscle strength and freedom from attacks of paralysis. His only complaint has been of occasional cramps in the muscles. Dietary sodium is no longer rigidly restricted.

Balance Studies

Sodium and potassium balance studies throw little light on the mechanism of action of spironolactone. Throughout the periods of administration the patient was in negative sodium balance. The estimated deficits (ignoring extrarenal losses) after five and ten days during the first course were 120 and 230 mEq. respectively, and after seven days of the second course 70 mEq. Fæcal sodium loss was measured over the first three days only, and it amounted to 3 mEq. per day. The true negative sodium balance therefore probably amounted to 26 mEq. per day during the first course, and to 13 mEq. during the second.

Potassium balance became positive during the first two days of spironolactone therapy on each occasion. The potassium retention amounted only to 30 mEq. and 20 mEq. respectively after forty-eight hours on the two occasions—i.e., less than the equivalent of a single dose of 4 g. of potassium chloride. The serum-potassium level remained in the normal range throughout, being no higher than on other occasions without medication.

Discussion

The primary defect in classical periodic paralysis is unknown. Now that a few cases have been studied in detail it appears that changes in potassium and sodium metabolism are too inconstant to be the basic abnormality (see for instance the metabolic dissimilarities between case 1 of Jones et al. 1959, and case 1 of Conn et al. 1957). Nonetheless they are obviously very important, and the speed with which an attack can be terminated by giving potassium chloride by mouth suggests a very important intermediary role for potassium. There are significant clinical and metabolic differences between periodic paralysis and primary hyperaldosteronism. In particular the fact that potassium is retained during attacks of periodic paralysis makes it extremely unlikely that they are due solely to intermittent hypersecretion of aldosterone. It is possible, however, that oversecretion of aldosterone is part of the mechanism of the attack and that its antagonism by spironolactone prevents the development of paralysis.

It is even more difficult to explain why administration of spironolactone should relieve the long-standing weakness between attacks. The possibility that our patient had in fact an aldosterone-secreting tumour was considered, but was rejected because of the length of history (twenty-four years) and the absence of hypertension, albuminuria, and hypokalæmia or alkalosis between the attacks. In primary aldosteronism striking natriuresis and potassium retention occur when spirolactones are administered (Kistler et al. 1959, Luetscher and Lieberman 1958, Salassa et al. 1958, Wrong and Gowenlock 1958), but these were not found in our patient.

The small changes in sodium and potassium balance seem insufficient to explain the obvious clinical improvement. Muscle strength was considerably improved after 48 hours, at which time the negative sodium balance and positive potassium balance were both less than 40 mEq. Much larger alterations in sodium and potassium balance have been induced by low-salt diet and administration of potassium chloride with less striking clinical improvement.

As far as we know, only one other patient with periodic paralysis has been treated with an aldosterone antagonist. Rowley and Kliman (1960) gave a patient short courses of SC 8109, a compound closely related to spironolactone and with similar actions. After the drug was given no consistent changes in electrolyte excretion were obvious from their balance data; but it was more difficult to provoke attacks of paralysis by withdrawal of potassium supplements or administration of 2-methyl-9-α-fluorohydrocortisone if SC 8109 was given simultaneously. These workers also considered their results " difficult to interpret ".

We conclude that, on present evidence, the beneficial effects of spirolactones are not explained by antagonism to the action of aldosterone on renal or enteric excretion of sodium and potassium.

These are not the only known actions of the spirolactones; they also lower blood-pressure in hypertensive subjects, and they have a sedative effect in large doses (Bartter 1960). Aldosterone affects magnesium balance (Hanna and McIntyre 1960) and resistance to shock (Bein and Jaques 1960); the extent to which these and other actions of aldosterone are antagonised by spirolactones has not yet been adequately studied.

Not only is periodic paralysis a rare disease but the patients are often unable to come into hospital for long-term investigation because of the danger of losing their precarious hold on their jobs. We know of only one other patient with classical periodic paralysis in the north-east of England, and she is not available to us for metabolic study. We therefore report this isolated example of a remission with spironolactone in the hope of stimulating further investigation of the actions of the drug by others with access to similar patients.

Summary

A patient with longstanding hypokalæmic periodic paralysis was treated with spironolactone. The severe intermittent attacks of paralysis to which he had been subject for twenty-four years ceased during treatment. Residual muscular weakness between attacks was also relieved and it recurred when placebo tablets were substituted for spironolactone.

Plasma-potassium level was not affected by treatment. Slight negative sodium balance and positive potassium balance were established on two occasions when spironolactone was administered, but the production of larger changes in sodium and potassium balance by other therapeutic measures did not result in commensurate clinical improvement.

We are indebted to Dr. Henry Miller for advice and encouragement; to Dr. T. M. Galloway for allowing us to study the patient; to Dr. A. Louis Latner for help with the biochemistry; to Dr. Margaret Irvine and Dr. Leo Kinlen for assistance with the metabolic studies; and to Sister M. J. O. Freeman and her staff for the dietary control. Supplies of spironolactone ('Aldactone') were provided by Messrs. G. D. Searle & Co.

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"It is interesting that technicians and scientists are rather time-bound. For instance, if Galilei and a modern astronomer, or Newton and a modern physicist, were to meet for, let us say, a television interview, Galilei and Newton probably would require several months' briefing before they could carry on confidently in such an interview. However, let us assume that Bertrand Russell, who is living now, and Kant and Plato, who have been dead for considerable time, would meet to carry out such an interview. After one half-hour of briefing they could probably communicate very well and meaningfully, because a philosophical analysis is a rather timeless undertaking."—H. E. LEHMANN, *Ann. N.Y. Acad. Sci.* 1961, **92**, 1038.

LISTERIOSIS IN FOUR SIBLINGS

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IN July, 1959, a district physician from southern Iceland came to ask for a necropsy on a boy of about 18 months. This was the third child of a 30-year-old farmer's wife; all three had died very young.

Her first child was a boy, born on Sept. 9, 1953. When he was 3 months old his parents suspected that something was wrong with him, and at 6 months he was taken to a pædiatrician, who did not find anything definite and told the parents that the child might improve. This boy died at the age of 14 months. He could not sit up or keep his head up. When he died, he had been feverish for a month, and antibiotics had seemed to have no effect. His outward appearance and habitus suggested mongolism.

A second child, a girl, was born on Nov. 9, 1954. She was weak from birth, and never cried; and she died when 10 months old, having been feverish for some months. This girl had a mongoloid appearance.

The third child, a boy, was born on Dec. 20, 1957. This child was the least sickly of the three. At the age of 3 months he was taken to the pædiatric department of the State Hospital in Reykjavik, and sent home after 3 weeks with a diagnosis of hydrocephalus. He died on July 9, 1959, and was brought here for necropsy.

All three children had seemed able to follow what was going on around them with their eyes, which would follow moving objects, but they did not move their head or body. They could smile and babble, but they never cried. Their dentition was normal. All seemed to have died of an intercurrent infection.

When the dead boy was brought here for necropsy the mother was pregnant for the fourth time. With her husband's consent she had applied for legal abortion with subsequent sterilisation, and this application had been granted.

Necropsy

We performed the necropsy on the boy on July 11, 1959. His body was 78 cm. long, and in fairly good condition. The head was large, the right side bigger than the left. When the skull was opened a striking asymmetry of the brain and skull was revealed: the left posterior fossa was considerably larger and deeper than the right. The left occipital lobe reached farther back than on the right; but neither occipital lobe appeared to stretch back normally, and the cerebellum was left uncovered. Microgyria was apparent in the posterior part of both lobes. The frontal gyri on both sides were large and broad (fig. 1).

The cerebral ventricles were not visibly distended. In the posterior part of both lateral ventricles some small protuberances were seen, about the size of the child's fingertips, slightly more yellowish than their surroundings. The height of these nodules was 1–2 mm. No sign of meningitis or adhesions was seen.

The internal organs appeared normal. In particular there were no abnormalities of the heart or large vessels. The liver weighed 315 g. and was of normal appearance, as were the bileducts and gallbladder. The spleen weighed 16 g., the right kidney 42 g., the left kidney 46 g., and the suprarenals 1·5 g. each; all were normal. The thymus weighed 5 g., and except for its small size was normal. The thyroid weighed 1 g., which is a usual weight in these parts.

In the intestinal tract, pancreas, bladder, and rectum there were no pathological changes. The right lung weighed 80 g. and the left 70 g. The posterior portions of both lungs were slightly firmer than normal, but not sufficiently so to justify a diagnosis of inflammation.

Fig. 1—Brain of third child.

On microscopic examination, no obvious inflammation of the meninges or of the brain was observed. In the left occipital lobe a dissolution of brain tissue could be seen in several places, and gliosis was apparent in others. In the medulla oblongata no pathological changes were noted. Perivascular infiltration was nowhere seen, except around a subcortical vein, where œdema and some monocytic infiltration was observed (fig. 2). The choroid plexuses appeared histologically normal.

In the liver and other internal organs no pathological changes were found except that, in the kidney, small microscopic calcifications were noted in some of the tubules of Henle's loops (fig. 3).

Fourth Pregnancy

The necropsy did not tell us why the child had died. As the mother was about 4 months pregnant and wanted to have an abortion performed, we arranged with the obstetric department for a cæsarean section to be performed and for the fœtus to be brought to us with the membranes intact.

This was done on Aug. 20, 1959, and we received the fœtus with intact membranes. Amniotic fluid (about 200 ml., somewhat turbid, and colourless) was withdrawn by puncture under sterile conditions. On direct microscopy of the centrifugate of this fluid, we observed gram-positive cocci, forming chains of two or more, and also gram-positive and gram-negative rods, slender and of various lengths, but averaging 2 μ, the shortest resembling coccobacilli.

Culture on blood-agar gave slightly convex, translucent, smooth, hæmolytic, colonies, which were subsequently identified as *Listeria monocytogenes*.

The cultures in bouillon were very motile, especially at room temperature, but much less at 37°C. The biochemical reactions were those of listeria: glucose+, lactose+, sucrose+, salicin+, maltose+, mannitol 0. No gas formation. Urea-agar negative. No formation of hydrogen sulphide. The amniotic fluid was examined again after being kept for 15 months in a refrigerator and listeria grew copiously from it, as before, and also *Streptococcus viridans*. The listeria culture was tested for sensitivity against antibiotics and sulpha compounds with 'Difco' discs:

Chlortetracycline	+++	Oxytetracycline	+++	Sulphafurazole	++
Chloramphenicol	○ –	Erythromycin	++	Sulphadiazine	++
Dihydrostreptomycin	+	'Triple sulpha'*	++	Sulphamethizole	++
Penicillin	++	Sulphasomidine	+++		

The fœtus looked normal and measured 20·5 cm; from blood from the heart a few colonies of *Str. viridans* were grown, which at the time were considered to be contaminants from outside. 4 mice were each injected intraperitoneally with 0·5 ml. of the pure-broth culture, and 2 guineapigs with 1 ml. each. None of the animals died; all were killed after 10 days. Cultures were made from the spleen and liver of all of them; but all were negative with the exception of the liver of 1 of the guineapigs, in which whitish nodules were seen.

The injections were repeated in a similar number of animals but the doses were doubled. Listeria was grown from the liver and spleen of 1 mouse, and from the liver of 1 guineapig.

* Triple sulpha ('Difco') contains sulphadiazine, sulphadimidine, and sulphamerazine.

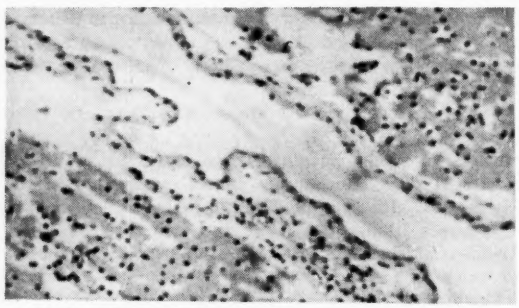

Fig. 2—Third child: inflammation around subcortical vein.

None of the animals was visibly ill. 2 pigeons were also injected, but without result.

In sections from the fœtus no changes of note were seen except in the liver (fig. 4). The lobular structure was disrupted, with great numbers of large, mononuclear cells between the strands of liver tissue, apparently exerting such pressure upon them that many of them were hardly visible. In the lung diffuse inflammation was noted; alveoli and interstitial tissue were infiltrated by mononuclear cells with a few segmented leucocytes (fig. 5). In the bronchioli there was much exudate and in some even epithelial proliferation.

In the placenta minute precipitations of calcium were found in some villi, and rod-shaped organisms were seen; but in cultures from vaginal smears and cervical secretion from the mother, no listeria was found.

Fifth Pregnancy

The physician who had told us of these cases was advised not to sterilise the mother, and not to discourage her from becoming pregnant again. We recommended that in a further pregnancy he should administer oxytetracycline to the mother, for seven days each month, in the third and subsequent months of pregnancy.

In December, 1959, the mother became pregnant again, and from the third month onwards oxytetracycline was given as we suggested. On Aug. 13, 1960, she gave birth to a girl, who looked normal, and very different from her previous babies. The doctor who attended the other three children says that this is the first child to show no signs of sickness, and the parents agree. This girl is now 10 months old, is normally developed, and was healthy in all respects when seen at the pædiatric hospital a month ago.

Discussion

Listeria monocytogenes was first described by Murray, Webb, and Swan (1926) as the cause of an epidemic in laboratory animals. Since then scattered reports of the disease in man and animals have been published from time to time in the past decade with increasing frequency,

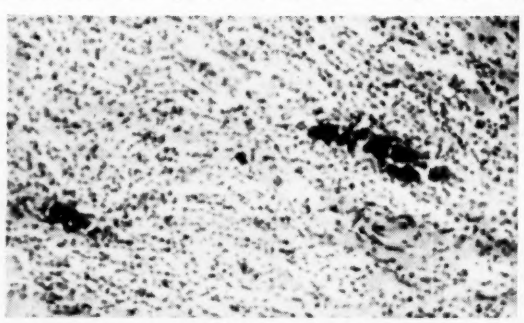

Fig. 3—Third child: calcification of Henle's loops of the kidney.

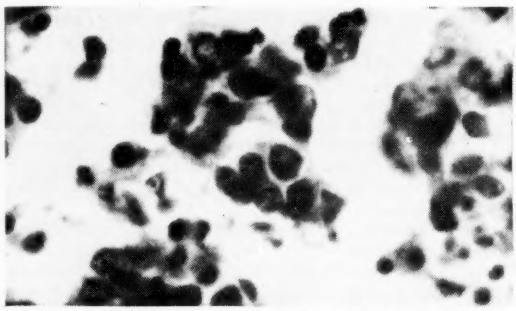

Fig. 4—Liver of fœtus (4th pregnancy). Note disruption of liver strands by monocytic cells.

so that listeriosis should no longer be considered a rare disease in man. It is also common in animals, especially in sheep.

We are indebted to M. L. Gray and his coworkers (1951, 1954, 1957) for their work on listeriosis in animals, and to Seeliger (1958) for his contributions to knowledge of listeriosis in man. Many workers have helped to elucidate the pathogenesis of listeria, and a good review of present knowledge is contained in a recent symposium (Roots and Strauch 1958). According to Flamm (1958) listeria can manifest itself in three different ways: (1) as a saphrophyte; (2) by causing local inflammation; and (3) by causing septic infections. Although many other organisms are known to vary greatly in their pathogenicity, few seem to be as unpredictable as listeria. In general the microorganisms appear only slightly pathogenic, especially for adults, but they can occasionally cause fatal septic infections. In man they are definitely more pathogenic for the fœtus and the newborn than for adults, and listeriosis is now thought to cause what used to be called septic granulomatosis in infants. The fœtus is infected through the placenta, where small foci of infection may be found; but, as a rule, the mother does not show any sign of infection. Sometimes she may have had an attack of pyelocystitis, in which " diphtheroid " organisms have been found, which may have been listeria.

It is noteworthy that animals can be infected by feeding with listeria-infected material only if they are pregnant (Trüb and Boese 1958); and pregnant women are in greater danger of catching the infection in hospitals than others. Yet the infection never seems to be fatal to the mother. In the newborn the disease may manifest itself as (1) a septic generalised infection, (2) meningitis, or (3) encephalitis or meningoencephalitis.

Generalised infection is represented by " granulomatosis infantiseptica " of the newborn. As these children have frequently aspirated infected amniotic fluid, they are cyanotic and often have convulsions. The bacteria may be cultivated from all organs where macroscopical or microscopical changes are found, also from the middle ear, bile, gastric juice, and meconium (Potel 1958). Gram-positive rods are always found in the meconium in these cases.

If the disease is diagnosed at birth it may be cured by antibiotic therapy. Increased knowledge of the disease has led to an improvement in the cure-rate from 4% in 1949–55 to 14% in 1956 (Potel, loc. cit.). But even in patients apparently cured, liver damage may have been so extensive as to lead to chronic hepatitis and cirrhosis.

The second most common effect of listeriosis is on the central nervous system. The meningitis is usually similar to other meningeal infections, but sometimes monocytes predominate. The sugar-content is definitely lowered. Without antibiotic therapy the prognosis in these cases is bad.

Listeria encephalitis carries a worse prognosis than the meningitis. It seems to have a predilection for the region around the fourth ventricle, the medulla oblongata, and the brain-stem, and perivascular cuffing by mononuclear cells may be seen. It may sometimes lead to hydrocephalus.

Trautmann and Götze (1958) reported the case of a woman who had a 10-year history of listeriosis, with stillbirths, thrombophlebitis, lymphadenitis, pyelitis, migraine, and finally epileptiform convulsions of the jacksonian type. Great improvement and lowering of the agglutination titre was observed after treatment with tetracycline.

Gray has suggested that women suspected of having listeriosis should be examined for monocytosis, since an increased monocyte-count has been found in animals after the birth of listeria-infected offspring. In man this phenomenon has not been observed.

Listeriosis may be rare in man, but it is possible and

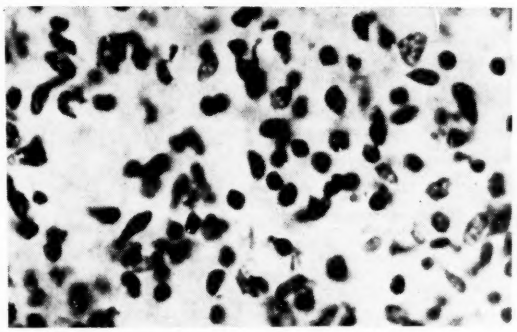

Fig. 5—Lung inflammation in the fœtus (4th pregnancy). Note the large number of mononuclear cells.

even likely, that listeriosis might be judged not to be so rare if we could find out how many people harbour the organism. Sheep-breeding populations are most likely to be affected; it is an established fact that listeria may cause a mastitis in sheep and cows, and pass into the milk, making unpasteurised milk a health risk; Gray (1958) has isolated listeria from goat's milk after 45 days' refrigeration. Listeria has also been found in meat, but danger from that source seems less likely. A striking characteristic of listeria is that culture succeeds better with material which has been refrigerated for weeks or months.

In Iceland we have had several epizootics of listeriosis among sheep, sometimes taking the form of abortions, at others sepsis or meningoencephalitis in newborn lambs, and also in adult sheep. It has also been observed in cattle, horses, and chickens. It is therefore not surprising that the disease should be found in man. The disease is by no means limited to rural areas: Gray found most of his cases in Michigan in industrial centres, particularly in Detroit.

In this country listeria organisms have been found by Pálsson (personal communication) in great numbers in silo-prepared hay, and especially in badly cured silage, with a pH of 6·0–7·3; and encephalitis in sheep is so often associated with this way of preparing hay that our farmers have been warned against silo-hay for sheep, although it appears to be harmless for cattle.

The report of Trüb and Boese (1958) from the Düsseldorf district in Germany, where in 1289 examinations of blood and tissues 24 cases of listeriosis were found in infants and adults, would indicate that it is not a rare infection. It may be the cause of habitual abortion, but how often it causes spontaneous abortions remains to be established.

The work of Rappaport et al. (1960) indicates that listeriosis may be a common cause of habitual abortions: they found listeria in the genitalia of 25 out of 34 women who habitually aborted and also in the fœtal tissues.

Summary

Three successive children of an Icelandic farmer's wife died when between 10 and 18 months old. They were thought to have a congenital brain malformation. A non-viable fœtus was delivered by cæsarean section in her next pregnancy; and *Listeria monocytogenes* was cultured from the amniotic fluid. In her fifth pregnancy she was treated with oxytetracycline. A healthy, living child was born. Listeriosis may not be as rare as is generally believed.

My thanks are due to Dr. Magnus Agustsson, Hveragerdi, who had the four children under his care and furnished the clinical data on them and on the mother.

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MENINGITIS
DUE TO LISTERIA MONOCYTOGENES

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Listeria monocytogenes is increasingly recognised as a cause of meningitis, but a confident diagnosis can be made only by a bacteriologist. Great care has to be taken in both the initial examination of a cerebrospinal-fluid (C.S.F.) smear preparation and in the original examination of the culture plates if this organism is not to be overlooked. The following patient was admitted to St. Tydfil's Hospital on Jan. 30, 1961.

Case-report

A man, aged 53, was comatose at the time of his admission to hospital, and very little history was available. His own doctor thought that perhaps he had had a cerebrovascular accident. A neighbour, who accompanied the patient, said that he had been ill during that day with frontal headache and vomiting.

Later more details were obtained from a sister-in-law, who said that 6 months previously he had fallen on his nose and had had postnasal hæmorrhage for 24 hours. She was not aware of anything suggestive of cerebrospinal rhinnorrhœa. The patient had then remained well until 3 or 4 weeks before the present illness, when he began to lose his appetite. 2 days before admission he felt too ill to sit up, and complained of severe headache and pain in the back of the neck. He started to vomit the next evening, and he lapsed into coma during the afternoon before admission.

His temperature was 101°F and pulse-rate 100 per minute. Meningeal signs were present, and he had ptosis of the left eyelid, but his fundi appeared normal. The right arm and right leg showed weakness; there were no changes in the tendon reflexes, and both plantar responses were flexor. Apart from a few rhonchi over both lung bases, no other abnormal clinical signs were found.

Lumbar puncture, performed on the evening of admission, revealed turbid C.S.F. which contained: polymorphonuclears 365 per c.mm., lymphocytes 260 per c.mm., protein 132 mg. per 100 ml., chlorides 731 mg. per 100 ml., and glucose 14 mg. per 100 ml.; no tubercle bacilli were seen on direct examination.

The blood-glucose was 180 mg. per 100 ml., and the peripheral white-cell count was 14,000 per c.mm. (polymorphs). Because, at this stage, the C.S.F. smears gave no very clear bacteriological diagnosis, the patient was given: streptomycin 100 mg. intrathecally; penicillin 1 mega-unit parenterally, followed by 500,000 units 4-hourly; and an initial dose of chloramphenicol 500 mg. parenterally, which was later reduced to 250 mg. 6-hourly.

On the day after admission (Jan. 31) the C.S.F. contained: polymorphs 950 per c.mm., lymphocytes 120 per c.mm., protein 210 mg. per 100 ml., and glucose 19 mg. per 100 ml. Because his condition had not improved, prednisolone was started in a dose of 20 mg. t.d.s. through a stomach tube, and a further intrathecal dose of streptomycin 100 mg. was given. The original C.S.F. cultures now showed a few colonies which when filmed and stained resembled diphtheroids.

The patient's condition still continued to deteriorate—his temperature swinging between 101° and 104°F—and he died on his 4th day in hospital.

C.S.F. Cultures

C.S.F. specimens taken before treatment and 12 hours later both grew a few colonies of diphtheroid-like organisms, which were sensitive to penicillin, streptomycin, chloramphenicol, erythromycin, novobiocin, and furaltadone, but insensitive to tetracycline and sulphonamide.

After the patient's death the original cultures were reviewed. The colonies on blood-agar showed β-hæmolysis, and it was now suspected that these organisms were *List. monocytogenes*. Further bacteriological investigation at the hospital laboratory and the Public Health Laboratory, Cardiff (by courtesy of Dr. R. W. S. Harvey) confirmed this suspicion:

Blood-agar.—Scanty growth of small convex entire-edged colony.
Gram-stain.—A small gram-positive rod-shaped organism showing pleomorphism.
Glucose-broth.—Growth occurred at 37°C and 22°C.
Motility.—Negative at 37°C; positive at 22°C (characteristic tumbling motion).
MacConkey's agar.—No growth after 24 hours.
Methyl-red and Voges-Proskauer.—Reactions negative.
Culture at 4°C.—Grows easily.
Culture on 6·5% salt-agar.—Growth on overnight culture.
Sugars:

Glucose—acid and no gas.		Arabinose	nil
Lactose	nil	Dulcitol	
Maltose		Trosital	
Rhamnose		Inulin	
Salicin—acid and no gas.		Mannitol	

A culture into a guineapig's conjunctiva gave the characteristic response described by Turner et al. (1958).

Necropsy

This showed a purulent meningitis with extensive exudate covering both cerebral hemispheres and cerebellum; there was pus in the sphenoid sinus but *List. monocytogenes* was not isolated from this. Moderate atheroma of coronary arteries, and some purulent mucus in the air-passages were the only other positive findings.

Source of Infection

Shortly before the patient's illness, a cat belonging to the

household had had a bite on its ear, and this had suppurated. Apparently the cat was apt to shake its head, and blood and pus had been found on the wall. The cat's injury healed in about a fortnight—before the patient first became ill. A month later the cat appeared perfectly healthy, without any external signs of infection. There was no history of recent illnesses in the household or contacts. Possibly the 6-month-old nasal injury had caused a fracture of the cribriform plate, despite the absence of C.S.F. rhinorrhœa.

Sudden Death of a Relative

We were also told that the patient's sister-in-law's brother's wife had stayed with the patient for some time on the day but one before he went into hospital (Jan. 29): and she died suddenly 3 weeks later (Feb. 18). We are indebted to Dr. Noel Dearnaley for details of his necropsy findings, this patient not having been seen before death, by her own doctor:

> The liver, which weighed 900 g., was pale, soft, and fatty; microscopically massive necrosis involved the whole organ. The spleen weighed 100 g. and appeared normal. Nephrosclerosis was present. The upper lobe of the right lung was consolidated, with diffuse hæmorrhage.

At the time of examination, the pathologist was not aware of the listerial infection in a contact, and no specific bacteriological investigation was undertaken.

Discussion

No conclusions can be drawn regarding the relationship of these two deaths; but the fact that necrotic hepatitis occurs in rodents and poultry, and also in human intrauterine listerial infection (Mackie and McCartney 1960), may be significant. Listerial meningitis has been reported previously by Gibson (1935), Wright and Macgregor (1939), Edmunds et al. (1957), Mair et al (1957), Turner et al. (1958) and Barrow and Pugh (1958); and in a review Finegold et al. (1954) listed twenty-six certain cases and eleven possible cases, adding two of their own. Since 1956, notifications of this infection (not necessarily all meningeal) from Public Health Laboratory reports have totalled twenty-two.

Most workers have found it impossible to trace the source of contact except that in neonatal cases the female genital tract has been suspect. Grey (1960) and Rappaport et al. (1960) discuss genital listerial infection as a cause of repeated abortion, and cite Seeliger's finding that 16% of the mothers who had had infants affected with *List. monocytogenes* had had stillbirths or previous abortions. Infection of the male genital tract is apparently rare (Librach and Seth 1961); Wenkebach (1953) recorded five cases and Grey (1960) cites this as the only positive evidence of such infection. Horn et al. (1960) isolated *List. monocytogenes* from a subphrenic abscess which followed splenectomy, and McCarty and Bornstein (1960) grew the organism from a terminal endocarditis in a patient without meningeal infection.

Cases of listerial meningitis may well be missed bacteriologically because the organism produces few colonies on original culture, and may be dismissed as a contaminant diphtheroid (Mair et al. 1957) . The antibiotic sensitivity is important clinically. In the present case the organism was sensitive to the penicillin and streptomycin which were given, together with steroids, but the patient did not recover. Because the meningeal exudate is thick and fibrinous and the early use of steroids should be of help. In this country, in cases of acute meningitis, it should always be possible to obtain C.S.F. for bacteriological study before treatment is started, and antibiotics (preferably penicillin, streptomycin, and chloramphenicol) may then be given until bacteriological diagnosis and sensitivity are obtained.

Summary

In a fatal case of meningitis due to *Listeria monocytogenes* no route of infection was traced, though the household cat may have spread the infection from a wounded ear. A relative who died suddenly may have had the same infection.

A plea is made for adequate bacteriological studies of cerebrospinal fluid before starting antibiotic therapy in pyogenic meningitis.

We are indebted to Dr. J. F. O'Connell for referring this patient; to Dr. J. N. Dearnaley for the postmortem report on the patient's relative; to Dr. Y. P. Shankar, the house-physician, and Mrs. A. Dawkins, the ward-sister, for their help in management; and to Dr. R. W. S. Harvey for his assistance in the bacteriological study, and for his advice and criticism.

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AUSCULTATION OF THE ABDOMEN IN SURGICAL PATIENTS

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MOST methods of management after abdominal surgery are based on the principle that handling, cutting, and sewing of the gastrointestinal tract are followed by a period of so-called " physiological ileus " in which forward propulsion is arrested; therefore, during this period it is necessary to withhold fluids by mouth and perhaps also to remove by gastric suction such secretions as accumulate. One of the clinical observations on which this principle rests is the occasional occurrence for several days after abdominal surgery of a very definite arrest of intestinal activity; this seems commoner when the upper gastrointestinal tract has been operated upon. This state of affairs is often associated, however, with other evidence of a disturbed recovery and may thus be a pathological response. It cannot be assumed that ileus is inevitable after uncomplicated abdominal operations. Much more information is required on postoperative intestinal motility in the patient who is recovering normally after a successful abdominal operation before " physiological ileus " can be assumed to be a component of normal convalescence and before any valid comparison can be made between the many techniques of postoperative management.

This paper analyses two simple indices of motility, both of which have been used before—the progression of barium out of the stomach (Porter 1948) and the pattern of intestinal noise heard on auscultation.

Barium Studies

40 ml. of thin barium solution was administered to 15 patients directly after partial gastrectomy and the distri-

bution of the radio-opaque medium studied by serial X-rays at 6, 20, and 36 hours. After 6 hours most of the barium was still in the gastric stump. At 20 hours much of it had left the stomach and was well down into the efferent loop and at 36 hours it had become scattered and much diluted in coils of jejunum and ileum. These preliminary results suggest that very shortly after an uneventful operation of this kind some form of forward propulsion, not necessarily normal, begins.

Abdominal Auscultation

Many surgeons place considerable reliance on the presence of audible peristalsis in the abdomen as a sign of intestinal contraction. There are some qualifications to this statement and even with refined methods of analysis such as have been attempted by some (Farrar and Ingelfinger 1955) auscultation cannot give more than very general information about intestinal motility. Because it is a method in clinical use for assessment of progress, however, it seemed worthy of investigation.

Method

In order to establish a normal pattern, sounds were recorded on a high-fidelity tape-recorder (Ferrograph, series 4) through a crystal microphone taped to the abdomen as near as possible to the umbilicus; the sensitivity of this combination is about the same as that of a normal stethoscope. Each record was of five minutes' duration. It was played back as often as necessary and the sounds analysed for type and minute frequency (in subsequent discussion the term "frequency" always refers to the minute frequency and not to the audio-frequency). This objective record was obtained not only to facilitate subsequent analysis but also to avoid the human error of perception of infrequent events (Mackworth 1950).

A sound was defined as a discrete noise or gurgle separated on either side by a period of silence. Such a description is incomplete in the presence of long-running sounds which, presumably, represent widely propagated waves of peristalsis. Surprisingly, such sounds are not common and they did not noticeably affect the general analysis.

Results of Auscultation

Records were taken from 15 normal subjects. The minute frequency varied from 5 to 34 sounds per minute with a few activities in excess of this, which must be regarded as continuous because the end of one sound and the onset of another cannot be distinguished. A frequency of 15–25 per minute includes three-quarters of the normal subjects. Some lower frequencies with longer runs, as already defined, may also be termed continuous but this is uncommon. Nearly every variety of sound described as typical of abdominal disorder has been heard from time to time in the normal abdomen although most sounds were "explosive", "dry", "moist", or peristaltic runs. The diagnostic value of the fine qualitative analysis of intestinal sounds is thus very much in doubt; nevertheless, in our opinion, the presence of a very high-pitched tinkling bowel sound is indicative of abnormal intestinal motility within dilated intestinal loops, although it is not necessarily diagnostic of the presence of mechanical obstruction. The frequency of sound is almost always reduced after food.

Little is known of the origin of intestinal noise. Cannon (1905) suggested that some sounds originated in the pylorus and if this is the case then it would be reasonable to assume that the ileo-cæcal valve might be another source. Studies of patients who had undergone total colectomy or total gastrectomy reveal, however, a normal minute frequency and type of sound, and it therefore seems likely that most intestinal noise originates in the small bowel:

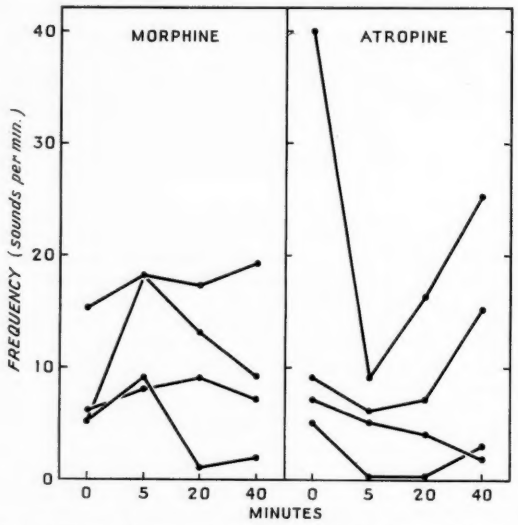

Fig. 1—Effects of intravenous morphine and atropine on frequency of bowel sounds in normal subjects (6 cases).

Operation	*No.*	*Frequency*	*Character*
Panproctocolectomy	2	26 and 22	Normal
Total gastrectomy	2	15 and 21	Normal
Upper radical gastrectomy ..	1	5	Normal

Further Factors which Influence Intestinal Sounds

Morphine and atropine were administered by intravenous injection in doses of 16 mg. and 0·6 mg. respectively. The effect is significant but transient (fig. 1) and has largely disappeared after 40 minutes. Morphine always increases the frequency and produces a dry type of peristaltic run, whereas atropine decreases the frequency and tends to produce single fluid sounds. With one exception all recordings were made shortly after meals and this accounts for their low initial frequency. Recordings under clinical circumstances were not made within the period of effect of these or other drugs.

It has been thought that a reduction in systolic blood-pressure below 90 mm. Hg. by depletion of the blood-volume results in silence in the abdomen (Dudley 1958). Peristalsis is certainly abolished in an isolated intestinal loop through which perfusion is reduced. On five occasions when recordings were taken under such circumstances, however, the sounds were within the range of normal frequency and type provided there was no intra-abdominal disease. This confirms the previous observations of Rob, who concluded that careful auscultation in the battle casualty was of considerable value in deciding for or against the

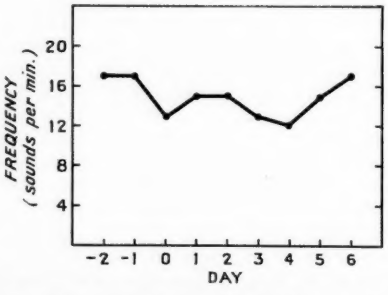

Fig. 2—Average curve for intestinal sounds after laparotomy and cholecystectomy.

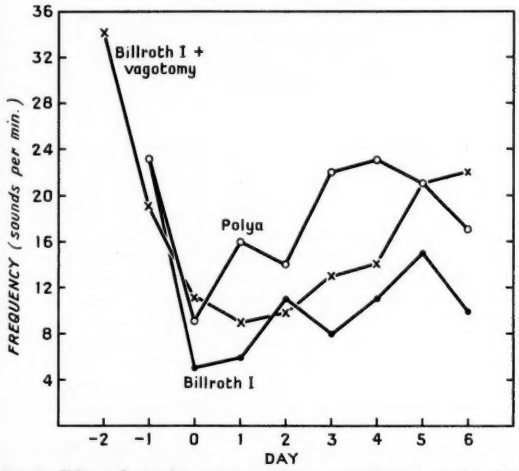

Fig. 3—Effect of gastric surgery on frequency of bowel sounds. Each line is average of 6 cases.

presence of visceral trauma (Rob 1947a and b).

Effects of Upper Abdominal Surgery

Four groups of six patients who made a normal convalescence were studied. The operations were: (1) laparotomy and cholecystectomy; (2) Billroth I gastrectomy; (3) limited Billroth I gastrectomy and surgical vagotomy; and (4) Polya gastrectomy.

The gastric operation in each case was undertaken for dudoenal ulceration. After laparotomy or cholecystectomy (fig. 2) there is little change in the bowel sound frequency or type, and the patient does not find any difficulty in retaining fluids by mouth from very shortly after operation. After the gastric procedures there is always a striking reduction in audible peristalsis: greatest in the Billroth I group and least in the Polya group (fig. 3). The greatest reduction was on the first postoperative day, but audible sounds were never absent at any time provided the postoperative course was uneventful. Although the reduction in frequency varied in the different groups of gastric procedures the average frequency of each group gives a similar pattern and can be compared with the average frequency pattern of all the patients recorded postoperatively (fig. 4). It can be concluded that noise is reduced, but certainly not abolished, by gastric surgery. It is not justifiable to assume that peristalsis remains unaltered. In fact, sounds heard on the first two postoperative days were of the single explosive type. Peristaltic runs were rare except in the laparotomy and cholecystectomy group.

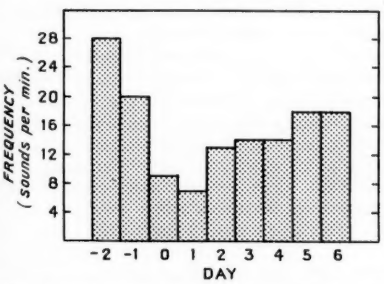

Fig. 4—Histogram of sound frequency in all patients submitted to abdominal surgery.

Sounds may disappear when there is delay at the stoma with distension of the gastric remnant, postoperative pancreatitis, or early adhesive obstruction. Instances of all these complications were encountered, but the sound frequency pattern recorded from them was excluded from the normal group. On several occasions when bowel sounds were being carefully studied the complete absence of noise heralded an abnormal incident before this had become clinically obvious.

Clinical Error

When sound frequency is low, careful auscultation is necessary, first to detect the sound and, secondly, to avoid the errors already described as inherent in listening to infrequent events. Analysis of the records on the postoperative patients showed that if the listening period is 20 seconds and the sound frequency 8 or less there is a 60% chance of not hearing sounds. Thus, in the first two postoperative days casual auscultation may fail to reveal sounds although these are present and this may account for the common clinical impression that they are absent after major abdominal surgery.

Discussion

The results suggest that some form of intestinal motility persists in the postoperative period. Further analysis by more refined techniques will be required to establish whether this peristalsis is effective, and work is proceeding along these lines. There seems to be sufficient evidence, however, to suggest that physiological ileus does not occur. One possible practical conclusion is that the uncritical use of naso-gastric suction in all upper abdominal cases should be reconsidered, and that it may sometimes be possible to rid the patient of the slight hazard and considerable discomfort of an indwelling tube. That this is so has been suggested by others (Eade et al. 1955) and we have confirmed it in our last 40 gastric operations in which intubation has been necessary only once. Our current technique in the management of a patient undergoing all types of surgery for peptic ulcer (other than gastroenterostomy and vagotomy) is to empty the stomach through a wide-bored tube at the end of the operation and then to leave him free from naso-gastric suction. Fluids and food are allowed at the end of 24 hours.

Auscultation of the abdomen is a reliable guide in management after an abdominal operation in that silence indicates some abnormality of convalescence. Although this may not be serious it always merits investigation and the silent abdomen may be the earliest warning sign. Normal sounds indicate satisfactory progress and they will usually be followed quite soon by the passage of flatus per rectum. But the passage of flatus cannot be considered valuable evidence of normal recovery because it is often so long delayed as to make this sign useless in controlling the oral administration of food or fluids. In 2 of our patients passage of flatus was strenuously denied until the seventh day after an uneventful gastric resection, although all the other indices, including auscultation, were quite normal.

Summary

A study of abdominal auscultation, by a method aimed at eliminating observer error, suggests that some form of peristalsis continues after an abdominal operation, although the frequency of bowel sounds is reduced. Naso-gastric suction may not, therefore, be needed as often as has been thought. The silent abdomen may be the earliest warning sign of an abnormality of convalescence.

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THE NATURE OF PENICILLIN RESISTANCE IN STAPHYLOCOCCI

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IT is generally accepted that there are at least two types of resistance to penicillin in staphylococci—the penicillinase type and the non-penicillinase. The penicillin-resistant staphylococci which infect our hospitals seem almost always to be penicillinase producers, and this type of resistance is thought to be the only one of serious clinical importance (Kirby 1945, Barber 1947, Spink 1951, Finland 1955). Laboratory tests, however, show that these penicillinase-producing staphylococci are not inherently highly resistant to the antibiotic: although large inocula can destroy large amounts of penicillin G, small inocula are quite easily inhibited by concentrations as low as 0·1 μg. per ml. On the other hand, by repeated subculture (or so-called "training") in the presence of subinhibitory levels of penicillin, it is possible in the laboratory to obtain, from a sensitive strain of *Staphylococcus pyogenes*, variants which are highly resistant to penicillin though lacking penicillinase. The resistance of these variants is of a more "personal" or individual nature than that of the penicillinase-producing strains, and it may be described as inherent or intrinsic resistance, since small inocula are almost as resistant as large inocula to high concentrations of penicillin. Penicillinase-producing staphylococci are usually fully virulent both to experimental animals and to man, whereas the non-penicillinase-producing variants obtained in the laboratory are often coagulase-negative and avirulent.

There is reason to believe that this picture is an over-simplification of a complex situation. The discovery of new penicillins which may profoundly modify the future range of penicillin treatment has stimulated new questions about the different mechanisms of resistance in staphylococci and about the relation between resistance to penicillin G and to other new penicillins—especially methicillin, which is resistant to the action of staphylococcal penicillinase. The results of experiments designed to answer some of these questions are here briefly reported.

Investigation

In most of the experiments inocula were prepared from eighteen-hour broth cultures of *Staph. pyogenes* diluted in broth. 0·02 ml. amounts of these were dropped on the surface of agar plates containing different concentrations of antibiotic. These were incubated for nine hours, recorded, reincubated for a further eighteen hours, and recorded again. The method was essentially that used by Demerec (1945, 1948) in his early studies on the nature of penicillin resistance to staphylococci. Serial subculture in liquid media containing increasing concentrations of antibiotic was used in some early experiments, but this was later abandoned because it gave no information as to the mechanism by which resistant variants arose, whether by survival of a very small number of cells from the original population or by a modification in the metabolic behaviour of most of the cells in the parent culture.

Penicillinase production was detected by a modification of the method of Manson et al. (1954) using cellulose acetate membranes (Knox and Smith 1961) and by estimating the destruction of penicillin G by means of the hydroxylamine method (Boxer and Everett 1949). The virulence of the various strains was compared by determining the L.D.50 using the intraperitoneal route in albino mice.

Experimental Results

It was reported earlier that a penicillinase-negative variant had been obtained from the penicillinase-positive strain of *Staph. pyogenes* E3 (Knox 1960). This penicillinase-negative strain (E3 P-) was sensitive to 0·02 μg. of penicillin G per ml. and to 1–2 μg. of methicillin per ml. It was coagulase-positive. It was of the same phage type and had the same virulence for mice as the original penicillinase-positive strain (E3) from which it was derived. About 10^7 cells from an eighteen-hour broth culture of this E3 P- variant were inoculated on a series of agar plates containing the following concentrations of methicillin: 0, 0·2, 1·0, 2·0, 2·3, 2·6, and 3·0 μg. per ml. The majority of the inoculated cells grew on 2·0 μg. per ml.; but on agar containing 3 μg. per ml. a few colonies grew rather slowly.

One of these was subcultured into broth and after overnight incubation serial dilutions of this culture were made and inoculated on a series of plates including higher concentrations of methicillin than those used previously—0, 1, 2, 3, 4, 5, and 6 μg. per ml. In this way a few colonies were obtained capable of growing in methicillin concentrations of 6 μg. per ml. By repetition of this process in successive experiments colonies were obtained capable of growing in concentrations of 25 to 30 μg. per ml. These were tested for their sensitivity to penicillin G and were found to be resistant to concentrations up to 10 to 20 μg. per ml. The variant isolated by this discontinuous process had thus increased 15- to 20-fold in its resistance to of methicillin, and about 500-fold in its resistance to penicillin G (without ever having been exposed to it).

These organisms, which though remaining coagulase-positive were found still to be penicillinase-negative, therefore represent an inherent type of penicillin resistance unassociated with penicillinase. The virulence for mice of this variant was no less than that of the parent strain.

In an earlier series of experiments the penicillinase-positive strain (the original E3 strain isolated from a clinical source) was subcultured repeatedly in broth containing increasing concentrations of methicillin. The E3 strain itself was sensitive to 3 to 4 μg. of methicillin per ml. whether a large or small inoculum was used. It was sensitive to about 0·1 μg. of penicillin G. per ml. when a small inoculum was used; but, being a penicillinase producer, it rapidly destroyed penicillin G in high concentrations when large inocula were used. This was shown by its ability to grow in these high concentrations and by chemical estimation of the rate of penicillin destruction by cell suspensions.

During repeated subculture, variants with increasing resistance to methicillin were isolated. One of these variants (E3 500) grew in methicillin concentrations of 500 μg. per ml. when a large inoculum was used, and in nearly as high a concentration, though slowly, when a small inoculum was used. Both large and small inocula were also resistant to penicillin G in concentrations of about 100 to 300 μg. per ml. This variant was found to have lost its penicillinase. No destruction of penicillin G could be detected by the hydroxylamine method when thick suspensions were used under conditions in which the original E3 strain was able to destroy penicillin G in concentrations of 2000 μg. per ml. in less than half an hour. The E3 500 variant was of the same phage-type (77) as the parent E3 strain. On nutrient agar it grew slowly, the colonies being small and poorly pigmented, and confluent growth was most vigorous at the periphery. Growth could be accelerated and improved by incubation in 10% carbon dioxide in air. This variant therefore produced colonies in some respects similar to the G colonies of staphylococci which have been described by many workers (Hale 1951, Wise and Spink 1954, Wise 1956). Its virulence for mice was significantly less than that of the parent strain, but it still remained coagulase-positive.

On several other occasions penicillinase-negative variants have been obtained from the E3 strain as the result of subculture in methicillin. Further experiments are being carried out to try to detect how and when this happens. It is, of course, well recognised that loss of penicillinase can occur rather erratically in penicillinase-producing cultures of staphylococci. It appears that methicillin is one of the agents which can accelerate this change, though the mechanism responsible is obscure.

Natural Resistance to Methicillin

It has previously been reported that a small number of strains of *Staph. pyogenes* were found to be naturally resistant to methicillin (Jevons 1961, Knox 1961, Rolinson 1961). On analysing the population structure of these strains it was found that they consisted of a minority of rather highly resistant organisms while the majority were only slightly more resistant to methicillin than the average strain of *Staph. pyogenes*. By repeated subculture on solid media containing increasing concentrations of methicillin, variants were selected from these original strains capable of growing up to 1000 μg. per ml. Most of the cells in cultures of these variants grew in this concentration. These strains remained coagulase-positive and penicillinase-positive, but the virulence to mice of a variant resistant to 1000 μg. per ml. was less than that of the original strain. The resistance of these strains to penicillin G was interesting. Small inocula showed "inherent" resistance to about 30 μg. per ml., while large inocula were able to destroy at least 1000 μg. per ml. The variants with increased resistance to methicillin including even the variant resistant to 1000 μg. per ml. were still only resistant to penicillin G in concentrations of about 30 μg. per ml. when a small inoculum was used, though again large inocula were able to destroy large amounts of penicillin by virtue of penicillinase. Thus in this case there was not a concomitant increase in inherent resistance to penicillin G.

Cross-resistance Between Different Penicillins

The fact that cross-resistance between different penicillins is not necessarily absolute is shown in the table, which gives the activity of six different penicillins against four strains of *Staph. pyogenes*—the E3 strain, the E3 500 (trained to be resistant to methicillin in the laboratory), 13137 (the naturally occurring resistant strain from Colindale), and 13137/1000 (obtained by serial subculture of 13137 on methicillin-containing media). The penicillins used were methicillin, penicillin G, penicillin V, phenoxyethyl penicillin ('Broxil'), phenoxypropyl penicillin (PA.248), and a new penicillin, α-aminobenzyl penicillin ('Penbritin', BRL.1341). With the E3 strain all the penicillins except methicillin showed the inoculum size effect so characteristic of penicillinase-producing staphylococci. The E3 500 strain showed inherent resistance to all the penicillins with all the inocula used. The Colindale strain 13137, although a penicillinase-producer, also showed inherent resistance with small inocula. The variant 13137/100 capable of growing in methicillin concentrations of 1000 μg. per ml. did not show any additional resistance to the other penicillins over and above the resistance shown by the parent strain 13137 itself.

Discussion

These experiments show that strains of *Staph. pyogenes* can show considerable variation in their resistance to methicillin and penicillin G. Strains resistant to methicillin always seem to show an increased inherent resistance to penicillin G. This is true both with variants obtained in the laboratory and in naturally occurring strains. This suggests that there is a basal level of "inherent" resistance to all penicillins whenever resistance to any one appears. But further selection of highly resistant variants capable of growing in methicillin concentrations up to 1000 μg. per ml. does not necessarily result in any further increase of penicillin G resistance above the original level of about 30 μg. per ml. In the laboratory experiments here described the fact that methicillin is resistant to staphylococcal penicillinase has made it a useful tool for defining even more sharply the distinction between the penicillinase and the non-penicillinase type of resistance in staphylococci. Both penicillinase-negative and penicillinase-positive strains can be trained to become resistant in the laboratory to methicillin. With penicillin G this is more difficult with penicillinase-positive strains which rapidly destroy it, and results are only clear-cut with penicillinase-negative strains.

These experiments throw no immediate light, and are not intended to, on the question whether clinically serious resistance to methicillin is likely to arise in the future. All the evidence so far suggests that if it does arise it will not be of the penicillinase type, since despite intensive search into many strains of *Staph. pyogenes* none have yet been found to destroy methicillin. Whether it will also prove to be of no clinical significance remains to be seen. There is every reason to believe that the strains naturally resistant to methicillin occur much less frequently than did strains resistant to penicillin G when it was first used.

The preliminary results of the mouse-virulence tests on these strains suggest that both the original E3 strain and the original 13137 strain naturally resistant to methicillin were virulent to mice. But whenever highly resistant mutants were obtained either by so-called "training" of the E3 strain in the laboratory or by "training" of the naturally resistant 13137 strain to higher levels of methicillin resistance this was associated with some loss of virulence. As has already been mentioned, in the case of the 13137 strain the additional methicillin resistance

CROSS-RESISTANCE BETWEEN METHICILLIN AND OTHER PENICILLINS. MINIMUM INHIBITORY CONCENTRATION (μg. per ml.)

Strain	Inoculum	Methicillin (celbenin)	Penicillin G	Penicillin V	Phenoxyethyl penicillin (broxil)	Phenoxypropyl penicillin (PA.248)	BRL.1341 (penbritin)
E3	15×10^6	7·5	>1000	>100	>1000	>1000	>200
	15×10^4	3·7	250	>100	250	62·5	200
	15×10^2	3·7	7·5	3·1	3·7	1·8	12·5
	15	3·7	< 0·9	0·8	1·8	< 0·9	6·2
E3 500	12×10^6	500	500	>100	500	1000	>200
	12×10^4	500	500	>100	500	1000	>200
	12×10^2	250	250	100	250	250	100
	12	125	125	50	31	250	50
13137	10×10^6	1000	>1000	>100	>1000	>1000	>200
	10×10^4	125	250	>100	250	250	>200
	10×10^2	31	62·5	50	250	125	50
	10	15	31	50	62·5	62·5	50
13137/1000	15×10^6	>1000	>1000	>100	>1000	>1000	>200
	15×10^4	>1000	250	>100	250	500	>200
	15×10^2	1000	62·5	50	125	250	50
	15	1000	31	50	62·5	62·5	50

Inocula: 0·02 ml. dropped on the surface of nutrient agar plates containing doubling dilutions of each antibiotic.

was not accompanied by a further increase in resistance to the other penicillins. The results of the mouse experiments do not justify us in assuming that methicillin-resistant staphylococci are avirulent in man; but the characteristics of the strain here described strongly suggest that staphylococci highly resistant to methicillin have much more in common with the non-penicillinase laboratory-trained penicillin-G-resistant staphylococci, which are relatively avirulent, than with the penicillinase-producing staphylococci which are certainly virulent to man.

In a paper published while this paper was in proof, Barber (1961) has described the characteristics of a number of strains of methicillin-resistant staphylococci. In the main her results agree with those reported here. Further experience, both in laboratory animals and in man, is needed before we can establish on a secure basis the significance of methicillin-resistant staphylococci.

Summary

Laboratory studies of methicillin resistance in cultures of *Staphylococcus pyogenes* have shown that variants resistant to methicillin, whether naturally occurring or artificially " trained " in the laboratory, were also resistant to all the other penicillins tested—benzyl penicillin (G), phenoxymethyl penicillin (V), phenoxyethyl penicillin (' Broxil '), phenoxypropyl penicillin (PA.248), methicillin (' Celbenin '), and a new penicillin (BRL.1341).

This increased resistance was of the intrinsic or inherent type, since small inocula were nearly as resistant as large to all the penicillins. It occurred independently of penicillinase activity since it was shown both by penicillinase-positive and penicillinase-negative strains.

A naturally occurring methicillin-resistant strain which was both a penicillinase producer and also inherently resistant to all the other penicillins showed no further increase in the inherent resistance to these even when " trained " in the laboratory to be resistant to methicillin concentrations of 1000 μg. per ml. Thus in certain circumstances an increased resistance to one penicillin is not necessarily accompanied by a corresponding increase in resistance to all the others. Preliminary experiments in mice suggested that resistance to very high levels of methicillin in *Staph. pyogenes* was associated with a decrease in virulence, and in the case of one variant with loss of penicillinase.

These observations suggest that resistance to methicillin in *Staph. pyogenes* cultures has more in common with the non-penicillinase type of resistance to penicillin G shown by laboratory " trained " cultures than with the penicillinase type shown by hospital strains.

Our thanks are due to Miss B. Whittamore for skilled technical assistance; to Dr. E. T. Knudsen, of Beecham Research Laboratories, for supplies of penicillin V, broxil, celbenin, and BRL.1341; and to Dr. J. K. Morrison, of Pfizer Ltd. for a supply of phenoxypropyl penicillin (PA.248).

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VASOPRESSIN-RESISTANT DIABETES INSIPIDUS ASSOCIATED WITH CYTOLOGICAL CHANGES IN THE SUPRAOPTIC AND PARAVENTRICULAR NUCLEI

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ALTHOUGH most cases of primary idiopathic diabetes insipidus respond to the antidiuretic hormone of the posterior pituitary, some are refractory to this therapy (Williams 1955). These atypical cases have been attributed to abnormalities in responsiveness of the kidney to the antidiuretic hormones (Waring et al. 1945, Williams 1946, Dancis et al. 1948, Soffer and Gabrilove 1951, Williams 1955, Wilkins 1957), since lesions have been found in the hypothalamicohypophyseal system in only a few cases of primary diabetes insipidus (Biggart 1937, Blotner 1958).

The following case of an infant with idiopathic vasopressin-resistant diabetes insipidus showed notable cytological changes in the supraoptic and paraventricular nuclei.

Case-report

CLINICAL RECORD

The patient, a white male infant, was born at term weighing 8 lb. 2 oz. after an uneventful pregnancy and delivery. During the next 6 weeks he failed to gain weight normally, and had intermittent fever. At 6 weeks he was admitted to hospital because of otitis media on the right. Coarse breath sounds were audible bilaterally. The urine had a specific gravity at or below 1·005. There was slight anæmia. Extensive bacteriological, radiological, and hæmatological studies were unrevealing. An intravenous pyelogram showed no abnormality. Although antibiotics were given, the fever persisted and the weight-gain was below normal. At $3^1/_2$ months, the patient was transferred to The New York Hospital for further studies.

The family history showed that the patient's mother, both grandmothers, and four paternal aunts had had polydypsia requiring 8–20 pints of fluid per day.

On admission to The New York Hospital his temperature was 38·6°C; other vital signs were not remarkable. The skin was pale, warm, and moist. A harsh systolic heart murmur was heard along the left sternal border. The edge of the liver was felt 3 cm. below the right costal margin. The patient reacted sluggishly to pinprick.

Hæmatological studies showed: hæmoglobin 7·9–10·5 g. per 100 ml.; red-cell count 2,250,000–3,140,000 per c.mm.; hæmatocrit 17–31%; white-cell count 8200–12,200 per c.mm. with a differential count of 53–83% lymphocytes; and platelet-count 80,000 per c.mm. The erythrocyte-sedimentation rate was 35 mm. in the 1st hour (Wintrobe). Urine analysis showed a specific gravity consistently below 1·009. A 24-hour urine specimen had a volume of 500 ml. (intake 795 ml.) and contained chlorides 11·4 mEq., potassium 3·5 mEq., and sodium 8·6 mEq. per 24 hours. Urea-clearance was 34·1% of adult normal (1st hour) and 28·1% (2nd hour). Urinary 17-ketosteroids were 0·6 mg. per 24 hours.

Blood-urea-nitrogen was 30 mg. per 100 ml. or lower. Serum chlorides ranged from 108 mEq. per litre when hydrated to 143 mEq. when dehydrated; sodium from 134 to 188 mEq. per litre; and potassium from 3·4 to 5·0 mEq. per litre. Blood sugar, calcium, and cholesterol, and serum-proteins were normal.

There was no response to vasopressin in amounts of 1 milliunit per ml. fluid intake, and the test was repeated a second time with similar results (table I). Injection of the same quantity of vasopressin from the same vial into another patient

TABLE I—VASOPRESSIN TEST ON PATIENT WITH DIABETES INSIPIDUS

Specimen	Date	Time	Intake (ml.)	Output (ml.)	Specific gravity	Urinary Cl (mg. per l.)	Urinary K (mg. per l.)	Urinary Na (mg. per l.)
1	Oct. 7, 1957	2.10 to 4.10 P.M.	50	50	1·001	21·7	12·8	18·0
2	,,	6.30 P.M.	85	67	1·001	20·7	15·3	23·2
3	,,	8.25 P.M.	90	30	1·001	18·5	17·6	21·9
4	,,	10.25 P.M.	90	21	1·002	19·9	24·4	20·7
5	Oct. 8, 1957	12.15 A.M.	90	40	1·002	18·8	17·4	13·5
6	,,	2.15 A.M.	90	86	1·001	16·9	11·1	18·3
7	,,	4.15 A.M.	90	86	1·001	18·8	10·3	19·0
8	,,	6.15 A.M.	90	80	1·001	32·5	10·5	18·5
9	,,	8.15 A.M.	90	106	1·001	45·2	13·4	28·0
10	,,	10.15 A.M.	90	71	1·001	37·3	16·2	29·2
11	,,	12.15 P.M.	90	61·5	1·001	34·7	11·2	25·5
12	,,	2.15 P.M.	90	68	1·001	29·0	5·3	23·4

Vasopressin infusion of 1 milliunit per minute (approximately) for 24 hours, with a total dosage of slightly less than 1 unit, had no significant effect on urine specific gravity, sodium concentration, or volume.

TABLE II—VASOPRESSIN CONTROL TEST ON ANOTHER INFANT

Specimen	Date	Time	Urinary output (ml.)	Specific gravity
1	Oct. 10, 1957	2.30 P.M.	155	1·002
2	,,	3.00 P.M.	137	1·004
3	,,	3.30 P.M.	67	1·003
4	,,	4.00 P.M.	14	1·030
5	,,	4.30 P.M.	39	1·015
6	,,	5.00 P.M.	118	1·006
7	,,	5.20 P.M.	245	1·004

Another patient given vasopressin from the same vial and in a similar manner as in table I. The response was normal.

TABLE III—INFANTS WHOSE PITUITARIES AND HYPOTHALAMI WERE STUDIED AS CONTROLS

Age (mos.)	Sex	Anatomical diagnosis	State of hydration
$2^1/_2$	M	Microcephaly, microgyria, and agenesis of corpus callosum	Poor turgor, skin dry; subcutaneous tissue sticky
4	M	Acute enteritis	Generalised anasarca
6	F	Multiple congenital anomalies of heart, lungs, and abdominal viscera	Slight pitting œdema of soft tissue of legs
15	F	Congenital hypoplastic anæmia	Not remarkable

used for control purposes showed a peak concentration of urine of 1·030 (table II).

2 days after discharge from the hospital, the patient was readmitted because of recurrence of fever and dehydration. Blood-urea-nitrogen rose as high as 56 mg. per 100 ml., but fell to normal levels after hydration. A low-salt diet and intravenous supplements of fluid were given. An electroencephalogram showed a normal sleep pattern; afterwards the patient developed respiratory distress for a brief time, and he died suddenly 8 days later on Jan. 3, 1958.

PATHOLOGICAL FINDINGS

Necropsy was performed 4 hours after death. For control purposes the central nervous systems and pituitaries from four infants, aged $2^1/_2$–15 months, were examined (table III). Microscopically, these showed no changes.

Fixation and Staining

Blocks of tissues from all principal organs were fixed in both Zenker's formalin and 10% formalin and were embedded in paraffin for routine sectioning.

The central nervous systems were fixed in 10% formal-bromide for at least 5 days. The hypothalami, including the entire supraoptic and paraventricular nuclei, were embedded in celloidin and serial-sectioned. The following stains were used: hæmatoxylin and eosin, Masson's trichrome method, Bodian's silver method for axon cylinders, the Weil-Loyez method for myelin, and Nissl's cresyl-violet technique.

The pituitary glands were fixed in Zenker's formalin, sectioned sagitally, and embedded in paraffin. The following stains were used: hæmatoxylin and eosin, Masson's trichrome method, Bodian's silver method, chrome-hæmatoxylin-phloxine technique, and Adams and Sloper's performic-acid/alcian technique (Adams and Sloper 1956).

Necropsy

The body was well developed and moderately well nourished, weight 11 lb. 6 oz. (5160 g.) and measuring 2 ft. (61 cm.) in total length (expected length 65 cm.). The configuration of the head was normal. The anterior fontanelle measured 3 cm. by 3 cm. The pale dry skin had poor turgor. The subcutaneous tissues were sticky.

The *lungs* together weighed 126·5 g. (expected weight 90 g.). The trachea and bronchi contained foamy yellow fluid similar to that expressed from the red-purple pulmonary parenchyma. Microscopically, the capillaries of the alveolar walls were hyperæmic and the alveoli contained pink granular eosinophilic material, with many macrophages. The dark red *spleen*, which weighed 12·5 g. (expected weight 19 g.), was unremarkable microscopically except for an occasional large histiocyte in the red pulp with finely vacuolated cytoplasm. The *adrenals* together weighed 3 g. (expected weight 4 g.). The thin cortices were light yellow and contained a scant amount of lipid stainable by oil red O. The *kidneys* weighed 40 g. (expected weight 60 g.). Grossly they were normal, but microscopically a few dilated capillaries were filled by homogenous red eosinophilic material—presumably thrombus. Careful examination of the tubules showed no notable cytological alterations. The glomerli and the arteries were structurally normal.

The *brain* weighed 770 g. (expected weight 691 g.). No gross lesions were noted on multiple sections. Microscopically,

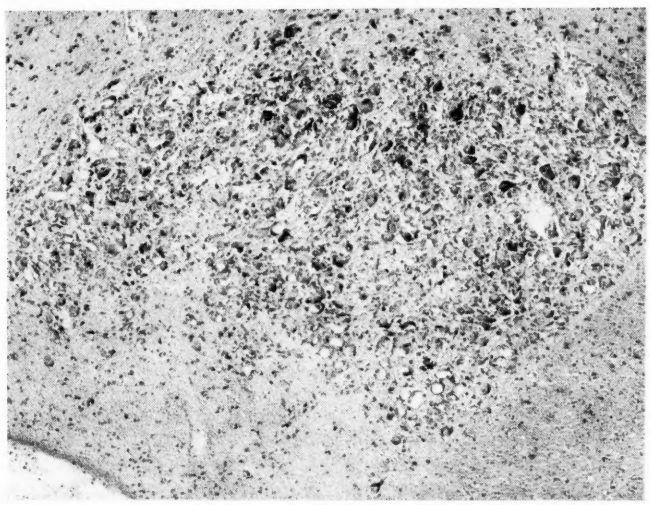

Fig. 1—Supraoptic nucleus; low magnification. (Hæmatoxylin and eosin. ×75.) Most of the cells of the nucleus are large, but other cells are also present.

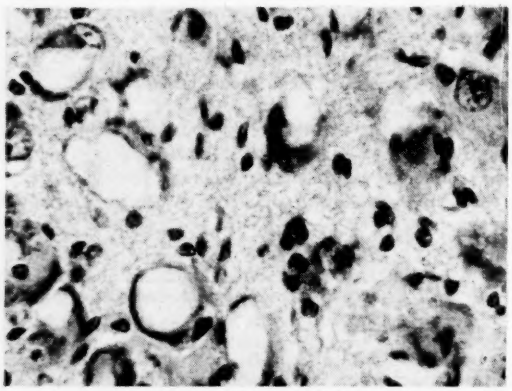

Fig. 2—Supraoptic nucleus; higher magnification. (H. & E. ×525.)
Many of the large cells show cytoplasmic vacuoles about which there is often deeply stained cytoplasm. The eccentrically placed nuclei have prominent nucledi.

the paraventricular and supraoptic nuclei contained normal numbers of neurons, but many of these were enlarged and had cytoplasm that often contained one or several large vacuoles in sections stained with hæmatoxylin and eosin (figs. 1–4). The cytoplasm in the centre of the cells was homogeneously eosinophilic, whereas that at the periphery was granular and basophilic. The cytoplasmic vacuoles were also clearly evident in those tissues stained with cresyl violet and by Masson's trichrome technique, the former showing Nissl's substance in the perphery of the cytoplasm. The stalk of the pituitary showed increased cellularity in sections stained with hæmatoxylin and eosin and Masson's trichrome (fig. 5). Hortega's silver carbonate showed many of these cells to be astrocytes and Bodian's stain showed a conspicuous decrease in the number of nerve-fibres in the hypothalamicohypophyseal tract, with some beading and fragmentation of residual axons (fig. 6).

The *pituitary* was not remarkable in sections stained with hæmatoxylin and eosin, Masson's trichrome, and Bodian's stains. Chrome-alum-hæmatoxylin/phloxine, and Adams and Sloper's performic-acid/alcian-blue stains showed deposits of material in moderate amount that stained like posterior-pituitary hormone.

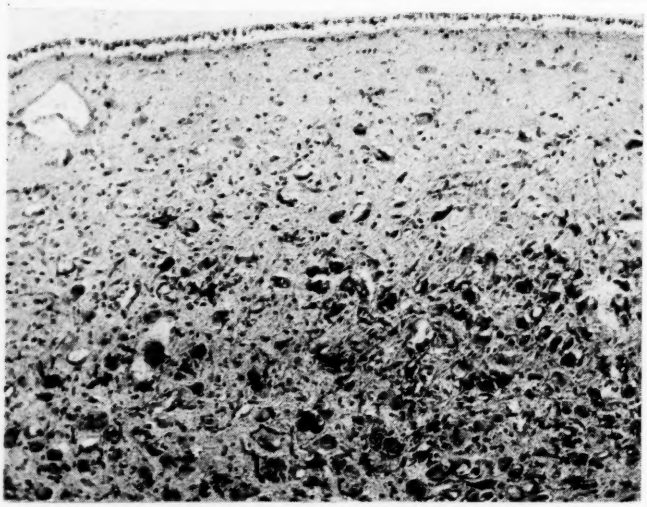

Fig. 3—Paraventricular nucleus; low magnification. (H. & E. ×100.)
Cytoplasmic vacuoles like those found in the supraoptic nuclei are evident at this magnification.

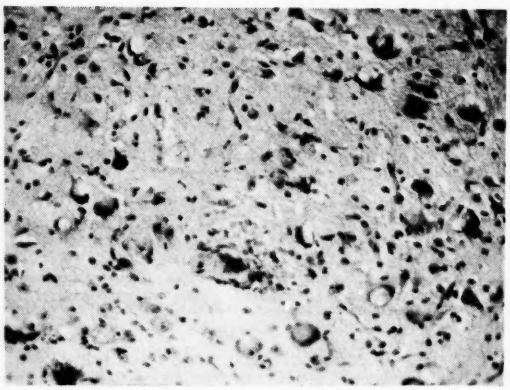

Fig. 4—Paraventricular nucleus; higher magnification showing cytoplasmic vacuoles. (H. & E. ×350.)

Discussion

An infant who died at the age of 7 months, after an illness characterised by fever, polyuria, low urinary specific gravity, and increased concentration of serum electrolytes, showed clinical features of vasopressin-resistant diabetes insipidus without other significant, evidence of renal disease. As in other reported cases (Waring, et al. 1945, Flax and Gersh 1955), postmortem examination failed to show notable anatomical changes in the kidneys. Neuropathological examination disclosed conspicuous changes bilaterally in the supraoptic and paraventricular nuclei. Great numbers of the neorons of these nuclei showed alterations. The number of axons of the hypothalamicohypophyseal pathway was diminished, and a notable astrocytic proliferation was present regionally about this pathway in the floor of the 3rd ventricle.

Cases of diabetes insipidus are customarily classified as primary or idiopathic, on the one hand, and as secondary or symptomatic, on the other. Idiopathic diabetes insipidus has been observed in both familial (hereditary) and non-familial (sporadic) cases. The few detailed post-mortem studies of such cases reported in the literature have shown marked loss of nerve-cells and increased numbers of astrocytes in the supraoptic and paraventricular nuclei (Blotner 1958). Symptomatic diabetes insipidus is not common (Soffer and Gabrilove 1951, Blotner 1958), and refers to those instances in which some specific disease—e.g., tumour, syphilis, trauma, or encephalitis—partially or totally destroys or interferes with the functions of the hypothalamicohypophyseal system. Forsman (1945) and Waring et al. (1955) cited cases of familial diabetes insipidus in which the administration of pituitary extract or vasopressin in usual dosages failed to result in normal concentration of urine. Such cases have been descriptively termed "nephrogenic" or vasopressin-resistant diabetes insipidus, and the clinical findings have generally been assumed to be secondary to hypothetical defects (anatomical or physiological) in the kidney (Williams 1946). Williams and Henry (1947) postulated an abnormality in the loop of Henle. It has also been suggested that a renal "end-organ" might be absent, abnormal, or

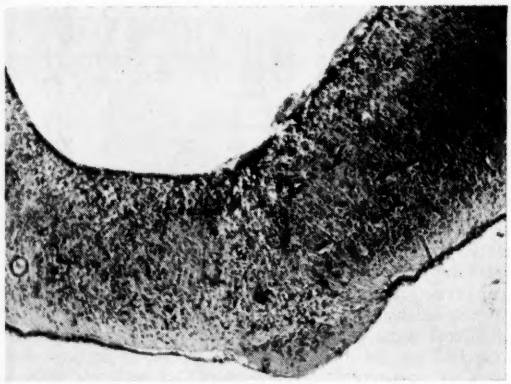

Fig. 5—Floor of third ventricle, showing a marked increase in the number of small cells. (Masson's trichrome. ×100.)

Fig. 6—Hypothalamicohypophyseal tract, showing a striking reduction in the number of axons. (Bodian's silver stain. ×100.)

defective (Dancis et al. 1948, Wilkins 1957). The nature of the hypothetical renal lesion, however, remains obscure. Apparently, thorough examination of the hypothalamico-hypophyseal system has been made in only a few cases (Biggart 1937) of secondary diabetes insipidus resistant to antidiuretic hormone. In his report Biggart (1937) suggested that a lesion in the tuberal nuclei, with or without damage to the supra-opticohypophyseal system, resulted in diabetes insipidus that was not controlled by antidiuretic hormone. In the present case of familial vasopressin-resistant diabetes insipidus, however, no lesions were evident in the tuberal nuclei.

Animal experiments (Fisher et al. 1938) have shown that, when the hypophysis or pars nervosa is removed in mammals, diabetes insipidus usually does not follow. On the other hand, when the supraopticohypophyseal nerve-tracts are merely sectioned, this condition does develop, but only in those animals with complete destruction of the supraoptic nerve-tract, supraoptic nuclei, median eminence, infundibular stalk, and pars nervosa. Polyuria, in laboratory animals prepared in this way, responds to vasopressin; and this indicates that in these the presence of intact supraoptic nuclei is not necessary for the activity of parenterally administered antidiuretic hormone. On the basis of these experiments, it was believed that the neurohypophysis produced hormone only so long as it was innervated by the supraoptico-hypophyseal tracts. But more recent studies (Leveque and Sharrer 1953) provide evidence that this hormone is synthesised in the supraoptic and paraventricular nuclei, and is transported along the axons of these neurons in the pituitary stalk to the pars nervosa.

Because the neurons of the supraoptic and paraventricular nuclei apparently synthesise antidiuretic hormone, the lesions described in these nuclei in the present case are noteworthy. Whether they caused the diabetes insipidus or resulted from hæmostatic changes secondary to fever, hæmoconcentration, or other aspects of the disease, remains unclear. Such cytological changes were not noted in the other infants studied, however, although one of these was dehydrated and another had anasarca at the time of death.

If these lesions were primary and antidiuretic hormone was not formed, the polyuria in this case would probably have responded to vasopressin given parenterally. Although the dosage of vasopressin was not increased to toxic levels in this case, as it was in others (Dancis et al. 1948, Williams and Henry 1947), a similar dosage of vasopressin from the same vial produced a normal response in another infant used as a control. The presence of normal antidiuretic substances in the urine of a patient with a similar condition was shown by bioassay in rats (Dancis et al. 1948). This last finding, moreover, militates against the possibility that the altered supraoptic and paraventricular cells in the present case might have produced an abnormal compound that failed to bring about anti-diuresis.

On the other hand, the cytological changes in the hypothalamic nuclei may possibly indicate an overproduction of normal antidiuretic hormone secondary to an unresponsive, or absent, renal " end-organ ".

Destruction of antidiuretic hormone before it reaches its site of action might also result in its overproduction. Soffer (1951) suggested that inactivation of hormone in the liver might be a mechanism in these cases. But it has been shown that plasma from a patient with vasopressin-resistant diabetes insipidus did not inactivate antidiuretic hormone at an accelerated rate (Williams and Henry 1947).

Both physiological and anatomical knowledge about vasopressin-resistant diabetes is still meagre, being largely limited to observation in single cases. No case reported to date has been thoroughly studied from both functional and structural aspects. Until extensive correlative clinical and anatomical studies are made in several cases, further interpretation and understanding of this disease process is not possible.

Summary

A case of vasopressin-resistant diabetes insipidus is described, which showed cytological changes in the supraoptic and paraventricular nuclei of the hypothalamus. The cells were enlarged and their cytoplasm was vacuolised. There were also decreased numbers of nerve-fibres in the infundibulum.

The pituitary was not structurally altered and special preparations demonstrated positive staining of hormone-like material in the pars nervosa.

No notable alterations were evident in the renal tubules; and the possible significance of the neuronal changes in relation to the pathogenesis of vasopressin-resistant diabetes insipidus is considered.

References overleaf

A MALE MONGOLOID WITH 46 CHROMOSOMES

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SINCE 1959, when Lejeune et al. described a characteristic karyotype with 47 chromosomes in mongoloid patients, other chromosomal variations have been reported (Fraccaro et al. 1960).

A mongoloid girl described by Polani et al. (1960) had 46 chromosomes, with a reciprocal translocation between nos. 15 and 22. Such translocations have been seen in cases of familial mongolism, with a chromosome number of 46 in the patients and of 45 in healthy relatives (Carter et al. 1960, Penrose et al. 1960). In this paper we are concerned with a mongoloid boy with similar cytological findings and a remarkable family history. A pedigree of the family is given in fig. 1; two sisters and a maternal aunt were mongoloids.

Case-report

The patient's father was born in 1915, and his mother in 1925, and both are healthy. The mother has no history of irradiation of the pelvic region. Her first pregnancy (1951) terminated in a spontaneous abortion. Three further pregnancies resulted in the birth of living children, all mongoloids.

When the children were born the mother was 27, 33, and 35. She had four siblings, all of them with the same mother but by different fathers. Three of the siblings are alive and healthy, and have one normal child each. The fourth sibling was a girl, born on April 17, 1928, and weighing 6 lb. 10 oz. (3000 g.). At 1 year she was admitted to a children's hospital where mongolism was diagnosed. She was seriously retarded mentally, and cyanotic. She died in hospital a year later, and the diagnosis was congenital heart-disease, mongolism, and hypothyroidism.

The patient's first sister, born on Aug. 27, 1952, weighed 5 lb. 2 oz. (2320 g.). The delivery was normal. A systolic heart murmur was audible, and she had typical signs of mongolism but no cyanosis. She died in the pædiatric clinic at the age of 23 days. Necropsy showed mongolism and congenital heart-disease.

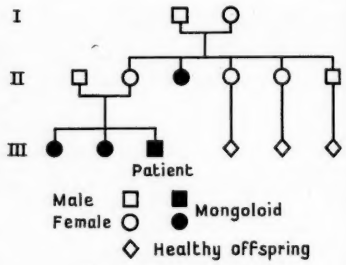

Fig. 1—The family tree.

The patient's second sister was born on June 8, 1958, and weighed 5 lb. 8 oz. (2500 g.). She became intensely icteric on the 4th day and was transferred to a pædiatric clinic. The heart was normal, but the patient had typical signs of mongolism. She died during an attack of cyanosis on the 10th day. The necropsy findings were mongolism, congenital heart-disease, and multiple cysts in the kidneys.

The patient was a boy, born on March 29, 1960, and weighing 6 lb. 12 oz. (3050 g.). Pregnancy and delivery were normal. The child was transferred to a pædiatric clinic because of feeding difficulties. Examination there revealed a flat face, with squat nose, oblique palpebral fissures, and protruding lower lip. There were obvious transverse palmar folds and hyperextensibility of the joints. His general condition declined, and he became extremely cyanotic, but examination of the heart revealed no abnormalities. He died at the age of 18 days. Necropsy showed mongolism, ductus arteriosus, and a patent foramen ovale, and purulent bronchitis with pneumonic areas in the lung parenchyma, and the abdomen contained an accessory spleen.

Cytological Observations

A biopsy specimen of the skin was cultured by the method of Bergman et al. (1959).

Most of the patient's cells had 46 chromosomes. Only 4 cells out of 59 had a deviating number, and this was probably due to technical errors. The following numbers were counted:

Chromosome nos.	..	..	46	47	48
No. of cells	..	..	55	3	1

The chromosome group 6–12+X comprised 16 chromosomes instead of the 15 typical of normal males. 14 of these chromosomes were readily matched into seven pairs, but not the other 2. 1 of these belonged to the longest of the group, while the other was of medium size (fig. 2).

Only 5 of the normal 6 big acrocentrics of group 13–15 were present. We could not decide with certainty which one of the pairs 13–15 was represented by a single chromosome. Observations on endoreduplicated cells indicated that the smallest member of the group, no. 15, was without a partner (fig. 3). In all other respects the karyotype was normal, the pairs 21–22 being complete, and the Y being easily identified.

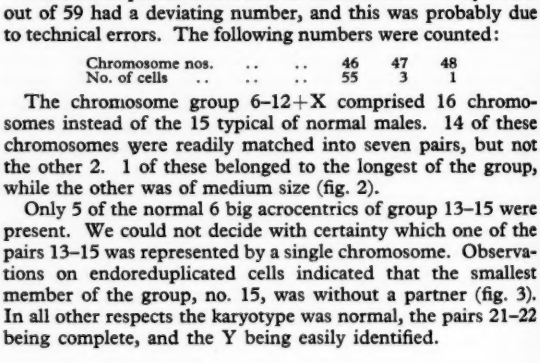

Fig. 2—Analysis of the karyotype of the patient.

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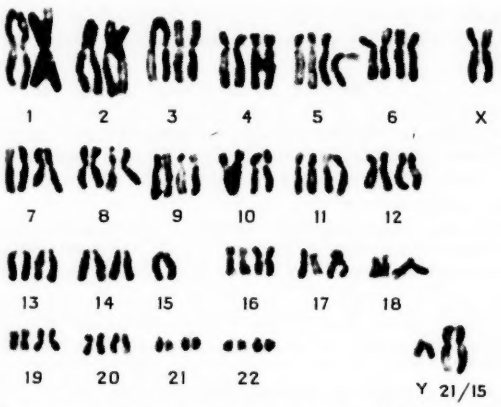

Fig. 3—Analysis of the karyotype of an endoreduplicated cell.

Discussion

As discovered by Lejeune et al. in 1959, and confirmed by several workers in different countries, the usual karyotype of mongoloids is trisomic for one of the small chromosomes of group 21–22. It is usually assumed that the larger one, no. 21, present in triplicate, is responsible for the mongoloid traits. Polani et al. (1960) found a chromosome number of 46 in a mongoloid girl. Karyotype analysis showed one chromosome of the group 13–15 (Denver nomenclature) to be missing, but there was an extra chromosome of the group 6–12+X—i.e., the same findings as in our patient. Polani et al. interpreted the deviation observed as a translocation between chromosomes 14 and 21 of the normal mongoloid karyotype. This explanation may hold for our case too. Thus, the two unmatched chromosomes of group 6–12+X may represent the X and the translocation chromosome 13–15/21.

Summary

A mongoloid boy is described, whose mother had two other mongoloid children and a mongoloid sister.

The patient had a chromosome number of 46 and a presumptive reciprocal translocation.

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LOUPING-ILL IN THE WEST OF SCOTLAND

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DURING recent years, the Russian spring-summer/louping-ill group of tick-borne viruses have become increasingly recognised as ætiological agents in acute infections of the central nervous system not only in Russia (Silber and Soloviev 1946) but in many parts of Europe (refs. cited by Svedmyr et al. 1958). In Britain, although louping-ill has been recognised for many years as an infectious disease of sheep (Pool et al. 1930, Alston and Gibson 1931, Macleod and Gordon 1932), natural infection of man with louping-ill has been reported in only 9 cases (Davison et al. 1948, Brewis et al. 1949, Lawson et al. 1949, Likar and Dane 1958). In these the clinical illness was a meningoencephalitis except for 4 described by Likar and Dane (1958) whose illness resembled acute paralytic poliomyelitis.

As no large-scale survey has been carried out in this country to determine the incidence of infection in humans, we have attempted to assess the importance of louping-ill in the west of Scotland by serological examination of patients with acute infections of the central nervous system.

Materials and Methods

The human sera examined came from 408 patients in the west of Scotland during the two-year period, January, 1959 to December, 1960: 374 had aseptic meningitis, (i.e., a non-paralytic illness with pleocytosis of cerebrospinal fluid from which no bacteria were isolated); 10 had a paralytic poliomyelitis-like illness in the course of which attempts to isolate enteroviruses had failed; 24 had encephalitis or meningoencephalitis. From all of these patients paired sera were received—i.e., one specimen of serum taken during the first week of the illness, and a second specimen taken in convalescence, generally ten to fourteen days after the first specimen. Sera were stored at −20°C. Before testing, they were inactivated at 56°C for thirty minutes.

Complement-fixation technique

A mouse-adapted laboratory strain of louping-ill was obtained from Dr. G. H. Edward, Wellcome Research Laboratories, Beckenham: for stock virus, aliquots of 10% infected suckling-mouse brain in 10% horse-serum saline were stored at −20°C.

The method employed for preparation of the antigen was based on that used by Porterfield and Rowe (1960) for louping-ill hæmagglutinins. Four-day old mice were infected intracerebrally with 10^{-3} or 10^{-4} dilutions of stock virus. When the mice were moribund, on the fourth to fifth day after inoculation, they were killed, and the carcasses were frozen at −40°C. They were then thawed out rapidly at 30°C, and the brains removed. An approximately 10% brain suspension was made in borate saline buffer, pH 9·0 (Clarke and Casals 1958), using a Ten Broeck grinder. An equal volume of the fluorocarbon 'Arcton 113' (I.C.I. Ltd.) was added, and the mixture homogenised in a M.S.E. masticator at maximum speed for three minutes. The extract was kept at 4°C overnight and then centrifuged at 10,000 r.p.m. in a water-cooled centrifuge. The supernate was removed and its pH adjusted to 7·2 to 7·4 with 1*M* disodium hydrogen phosphate. To destroy infectivity it was then incubated for two hours, at 37°C., with β-propiolactone to a concentration of 0·28%, and the pH was again adjusted to 7·2–7·4 with 1*M* disodium hydrogen phosphate. Sodium azide was added to a concentration of 0·08%, and the antigen stored at −40°C. Control antigen was prepared in the same way from uninfected mice.

The optimal dilution of each batch of antigen was determined by chessboard titration against positive human louping-ill antiserum: optimal antigen titre ranged from 1/8 to 1/24. Specific sheep or rabbit antisera were not used as standard sera because it was found that the antigen gave higher titres with these than with positive human serum.

Complement-fixation tests were carried out in plastic plates with 0·1 ml. volumes each of antigen in optimal dilution, serum dilution, and complement (four 50% hæmolytic doses). Dilutions of all reagents were made in barbitone-buffered saline. After standing at 4°C. overnight, the plates were placed at 37°C. for thirty minutes, and then 0·1 ml. 2% optimally sensitised sheep cells was added to each cup. The plates were left for a further forty minutes at 37°C., and were shaken at fifteen thirty, and forty minutes; and then allowed to settle at room temperature before reading.

Results

Of the 408 patients only 1 showed serological evidence of infection with louping-ill. This patient, a sheep farmer with meningoencephalitis, was under the care of Dr. P. McKenzie, Belvidere Hospital, who has already given a clinical description of the case (Combined Scottish Study, 1961). Specimens of the patient's sera on the 24th, 42nd, and 49th days, and 4 months, from the commencement of the first phase of the illness, gave C.F. titres of 32, 64, 16, and < 2 respectively. Confirmation of these results was provided by Dr. J. S. Porterfield, National Institute for Medical Research, who carried out hæmagglutination inhibition tests on the first two specimens and obtained titres of 320 and 640 respectively.

Discussion

From our findings it would appear that in the west of Scotland louping-ill infection of man played little part in acute infections of the central nervous system during 1959–60. Similar conclusions were reached by a small preliminary investigation in 1956–57 (Grist et al. 1960). However, during 1959–60, louping-ill was a serious disease of sheep in this area. Wilson (1961) has reported that, despite vaccination, there has been an increasing incidence of louping-ill infection in sheep in south-west Scotland including Argyllshire, culminating in several large outbreaks in the spring of 1960 with the death of many lambs and some sheep. The presence of louping-ill was confirmed by histopathological examination of brain specimens from affected animals and/or mouse inoculation. Serological examination also revealed a high incidence of louping-ill infection in lambs and ewes in this area (Gordon Smith 1961). Central Scotland was apparently unaffected as we found no evidence of louping-ill antibodies in sera collected from 204 sheep and 314 cows in Stirlingshire from August to November, 1960.

The high incidence of infection in sheep in south-west Scotland coinciding with the rare occurrence of signs of human infection in this same area would suggest that natural infection of man by tick bites is rare, probably requiring heavy infestation by the tick *Ixodes ricinus* which transmits the virus. On the other hand, infection of laboratory workers with louping-ill is not uncommon (Rivers and Schwentker 1934, Edward 1948). This would suggest that inhalation or ingestion of airborne droplets containing infective particles may be more important routes of infection than tick bites. However, virus dosage must be considered and this could be much greater in the laboratory than under natural conditions of infection.

That infection of humans with louping-ill can occur without symptoms of disease of the central nervous system has been reported in laboratory workers by Rivers and Schwentker (1934) and in abattoir workers by Lawson et al. (1949). Thus, although we have shown that in the west of Scotland louping-ill is of negligible importance as an ætiological agent in acute infections of the central nervous system, field serological surveys might bring to light cases who have had subclinical infection or an infection with signs and symptoms outwith the central nervous system. For such surveys complement fixation is most practicable; the non-infective complement-fixing antigen employed in the present study was simple to prepare and safe, and did not give non-specific reactions.

Summary

Sera from 408 patients in the west of Scotland suffering from either aseptic meningitis, encephalitis, or meningoencephalitis, or from " paralytic poliomyelitis ", during the two-year period, 1959–60, were examined for louping-ill antibodies by complement fixation using a mouse brain antigen.

Only one patient, a sheep farmer with meningoencephalitis, showed evidence of louping-ill infection.

During the period of study, louping-ill was a serious disease of sheep in part of this area. Thus, it appears that in Scotland natural infection of man with involvement of the central nervous system is rare.

We wish to thank Dr. J. S. Porterfield of the National Institute for Medical Research, Mill Hill, London, for much helpful advice on preparation of the antigen. We also wish to thank Dr. A. L. Wilson of the Veterinary Investigation Department, Auchincruive, Ayr, and Dr. C. E. Gordon Smith of the London School of Hygiene and Tropical Medicine, for helpful information on louping-ill in sheep in South West Scotland. We are grateful to Mr. W. Grant, veterinary officer for Stirling, for collection of sera from sheep and cows.

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Preliminary Communication

SPIRONOLACTONE IN THE TREATMENT OF MYASTHENIA GRAVIS

In 1934 Feldberg and Vartiainen [1] showed that the addition of potassium chloride to a perfusing solution stimulated the cells of the superior cervical ganglion of the cat. Smaller doses of potassium chloride, inactive alone, raised the activity of ganglion cells to preganglionic stimuli, to acetycholine, and to other chemical stimulants. These observations led Laurent and Walther [2] to try potassium in myasthenia gravis in the hope of an action at the myoneural junction similar to the one already shown at the synapses of a ganglion. They reported that large doses of potassium chloride (10–12 g.) by mouth gave a demonstrable improvement in myasthenia and that small repeated doses were a useful adjuvant to neostigmine.

Though the rapid excretion of potassium and its unpleasant side-effects when given in large doses have been a drawback to the use of potassium in myasthenia, it is still recommended, especially in severe relapses when neostigmine appears to have lost its effect.[3]

Last October it occurred to one of us (B. G.), when treating a woman of 58 with severe myasthenia, that the aldosterone antagonist spironolactone would be worth a trial because it diminishes the excretion of potassium.

The patient was bedridden, had difficulty in speaking and swallowing, and required injections of neostigmine as well as oral doses of pyridostigmine 360 mg. and neostigmine 120 mg. in 24 hours. After 3 days on spironolactone (400 mg. daily) she was able to walk and use her arms more easily, and her chewing and swallowing had also improved. Moreover, colic

1. Feldberg, W., Vartiainen, A. *J. Physiol.* 1934, **83**, 103.
2. Laurent, L. P. E., Walther, W. W. *Lancet*, 1935, i, 1434.
3. Dunlop, D. M., Davidson, L. S. P., Alstead, S. Textbook of Medical Treatment. Edinburgh, 1959.

and diarrhœa resulted while still on the same dose of neostigmine and pyridostigmine, suggesting a potentiation of the neostigmine effect. Spironolactone was stopped on two occasions and a relapse occurred each time within 2 days. Further studies with this patient were cut short because she returned home to Australia; but 5 months later news was received from her physician and from the patient herself that the benefit from spironolactone was maintained.

We have since treated six patients with spironolactone and a definite improvement was noted in five of them. The patient who noticed no benefit was a woman enjoying a marked remission and able to do some clerical work as well as her full housework. She was already so well that her symptoms were unaltered when she added spironolactone to her usual dose of pyridostigmine, of which she took 4 tablets four times daily.

A double-blind trial was carried out on two severely affected patients.

ILLUSTRATIVE CASES

CASE 1.—A single woman aged 45. Myasthenia was diagnosed at the age of 19 in 1934, with difficulty in chewing and swallowing as the presenting symptoms. Later ptosis, diplopia, and weakness of facial muscles became evident. Weakness of the limbs was also noted. In 1942 thymectomy was carried out without any obvious benefit. She has since taken 16 neostigmine tablets daily. She retained a fair measure of independence, doing part-time work until 1958, since when her condition had deteriorated. By this time she was unable to walk out of doors by herself and had difficulty with her bath and in writing letters. She became breathless on the least effort.

She was put on spironolactone in April, 1961, and improvement occrred within 2 days. She was able to lift her arms above her head and to walk unaided out of doors. She could squat on her heels and get up unaided. Although she is still considerably better on spironolactone than previously she is not quite so well as she was during the first weeks on the drug.

A double-blind trial began on June 16. The patient received spironolactone or inert tablets at weekly intervals, neither she nor the physician being aware of the nature of the tablets being currently given. In each of the three test weeks she correctly guessed what treatment she was having. It was especially interesting and convincing that improvement on spironolactone continued for 2 or 3 days after discontinuing the tablets. This continuing action has already been observed when spironolactone has been used as an aldosterone inhibitor. This patient felt that when on spironolactone she had " a sensation of well-being and self-confidence ". During the periods on the drug, but never on the placebo, she found that she could raise her arms above her head, and could extend her legs while sitting in a chair, for appreciably longer periods.

CASE 2.—A widow aged 53. At the age of 24, after a miscarriage, she noticed progressive weakness of her arms. She later developed diplopia, ptosis, and dysphagia. Thymectomy was performed in 1942. Ptosis, diplopia, and facial muscles improved after the operation. Her limbs, however, became progressively weaker, and even on 14 tablets of neostigmine and 7 of pyridostigmine daily she was unable to dress or feed herself or walk more than 100 yards. When seen by us she had marked diplopia and could not get out of a chair unaided. After 3 days on spironolactone she reported some improvement, particularly in walking, but her arms were unaffected. (She was a very unusual myasthenic in that she had gross wasting of her upper limbs.)

In a double-blind trial lasting 3 weeks she reported definite improvement on the 3rd day on spironolactone. She noticed a sensation of wellbeing, could walk longer distances, and could stand unaided from a sitting posture for the first time for years. When this treatment was stopped the improvement was maintained for 2 days; on the 3rd and 4th days she was weaker than she had been before taking the drug, but from the 5th day onwards she was back to her original level. During the trial she knew each time within 24 hours whether she was receiving the drug or the inert tablet.

A third patient deserves special mention.

A young married woman, 25 years old, had ptosis, diplopia, and occasional falls due to a sudden giving way of her legs. Apart from an injection of neostigmine to confirm the diagnosis, she has been treated for two months on spironolactone (400 mg. daily) for periods of a fortnight alternating with similar periods on no treatment. Her symptoms have remitted completely under treatment and recurred within 3 days of omitting the drug.

CONCLUSIONS

Spironolactone 100 mg. four times daily definitely improved six out of seven myasthenic patients. A double-blind trial in two severe cases supported this finding.

We have not yet had the opportunity to extend the double-blind trials, but our results suggest that spironolactone deserves wider use in myasthenia. In case 1 some partial resistance seemed to develop 10 weeks after treatment began.

We are planning investigations on potassium excretion and muscle content of potassium with our patients on and off treatment.

We are grateful to Dr. Denis Brinton and Dr. J. Clifford Firth for observations on patients under their care. Our thanks are also due to Dr. G. R. Venning, of Searle & Co. Ltd., for supplies of spironolactone (' Aldactone ') and of inert tablets of identical appearance and taste, and to Mr. J. R. Griffiths, chief pharmacist, St. Mary Abbot's Hospital, for his cooperation in the double-blind trial.

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Physician West London Hospital, London, W.14 — L. P. E. LAURENT, M.D. Lond., F.R.C.P.

Reviews of Books

Hemoglobin and its Abnormalities

VERNON M. INGRAM, PH.D., associate professor of biochemistry, Massachusetts Institute of Technology, Cambridge, Mass. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961. Pp. 153. 60*s*.

ONE of the most important contributions to biochemical genetics was made by Dr. Ingram when he discovered that the difference between normal and sickle-cell hæmoglobin was in one aminoacid, which in sickle-cell hæmoglobin was valine and in normal hæmoglobin glutamic acid. As normal and sickle-cell hæmoglobin were known to be inherited as mendelian characters this indicated that the action of a gene consisted in altering just one of many aminoacids in a complex protein molecule. This small monograph describes the background and the consequences of Ingram's classical experiment. The chemistry and architecture of globin are lucidly described and are related to the work on the three-dimensional structure carried on at the Cavendish Laboratory in Cambridge. Details of peptide chains are summarised, and an attempt is made to explain thalassæmia as an abnormal hæmoglobin disease in which the hæmoglobin cannot be differentiated from normal hæmoglobin by current methods. This is an excellent résumé: but for its price of almost 5*d*. a page, it would be, deservedly, a best-seller.

Introduction to The Clinical Laboratory

ROBERT P. MACFATE, CH.E., M.S., PH.D., chief, Division of Laboratories, Board of Health, City of Chicago; director of laboratories, Municipal Contagious Disease Hospital, Chicago; senior scientist (R), United States Public Health Service. Chicago: Year Book Medical Publishers. London: Interscience. 1961. Pp. 436. 75*s*.

DRAWING on thirty years' experience, Dr. MacFate has written a book for the trainee in a clinical laboratory, giving pride of

place to daily problems which concern the inexperienced. Thus he has written, not a book of methods (comparatively few procedures are given in extenso), but one in which important laboratory techniques such as titrations, weighing, and bacteriological transfer are dealt with in considerable detail. Suggestions for basic equipment are included, and advice is given on how to order and store supplies. Attention is even given to the appearance of the technician: "Neatness, cleanliness and good taste in dress and in action are desirable attributes". This manual covers aspects of training which are not included in the usual textbooks; but basic chemical, microbiological, serological, hæmatological, parasitological, and histological procedures are not ignored. There are also valuable chapters on the use of animals in clinical laboratories and on rules of safety and first-aid. There has hitherto been no book quite like this, and Dr. MacFate has filled the gap most successfully.

Animal Parasites in Man

N. H. SWELLENGREBEL, PH.D., M.D., professor of parasitology, the Royal Tropical Institute, Amsterdam; H. M. STERMAN, M.D., public health physician, Tropical Disease Diagnostic Service, Bureau of Preventable Diseases, New York City Department of Health; associate physician in tropical diseases and parasitology, Knickerbocker and Elmhurst General Hospitals. Princeton, New Jersey, and London: D. van Nostrand. 1961. Pp. 652. 67*s*. 6*d*.

THIS book is based on an earlier volume first issued over sixty years ago. It has been rewritten and enlarged and now appears in English for the first time. The material has been rearranged, the sections on diagnosis and drug treatment have been enlarged, and there are six new chapters on laboratory equipment and diagnostic methods. All these additions will be useful to all types of reader; but the rest of the text seems to be more suitable for the medical student than for biologists, for it does not go beyond the more important species of parasites found in man and it does not cater for readers looking for the range and depth of information given by other books on this subject.

Adrenergic Mechanisms (London: J. & A. Churchill. 1960. Pp. 632. 70*s*.).—This Ciba Foundation Symposium (held jointly with the Biological Council's Committee for Symposia on Drug Action) makes a large book, but as usual it has been well produced remarkably quickly. The subjects were many and interesting, and Sir Henry Dale gave a fascinating opening address on some of the history of the subject. The aspects discussed were the formation and fate of adrenergic transmitters, their storage, the neurones concerned, and the peripheral and central effects and mode of action in man and animals. Perhaps the most interesting sections are those on the effector cells on which the transmitters act and the mechanism of action of other sympathomimetic amines. In these sections appears much of the most recent work on the metabolic as well as the neurotransmitter actions of these amines; at last some more satisfying explanations are given of the apparently anomalous actions of adrenaline, and how it comes that at times this substance induces smooth-muscle contraction, and at others relaxation in the same muscle. This part of the book repays careful consideration, but it would be less than justice to suggest that the other excellent communications are not also worthy of attention. The volume was edited for the British Pharmacological Society by Dr. J. R. Vane and for the Ciba Foundation by Dr. G. E. W. Wolstenholme and Miss Maeve O'Connor.

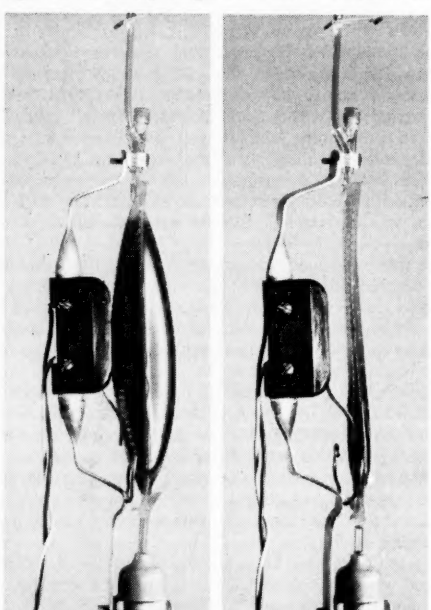
Roxburgh's Common Skin Diseases (12th ed. London: H. K. Lewis. 1961. Pp. 504. 50*s*.).—Dr. Peter Borrie has hearkened to the critics of his first revision of this famous textbook in 1959. He has altered the sequence of chapters and rewritten some, notably those on eczema and dermatitis. He has replaced many of the old illustrations whose blocks were worn out, though a few remain that might also go. Criticism concerns only details. Mesulphen is mentioned although it is no longer obtainable; and, although crotamiton is described as an antipruritic, its original use as a sarcopticide is not described. And does penicillin cure erysipeloid in a few days? The figure on p. 81 must refer to *Microsporum* and not *Trichophyton* infection. Elsewhere there are irritating misspellings, some repeated—Beznier, Hennoch, scurvey, hæmosidirin, xanthamatosis. The use of capitals, bold print, and italics seems inconsistent and is therefore unhelpful. Abandonment of the apothecaries' system and symbols would be in keeping with modern practice. Despite its faults, this book remains the best for the undergraduate student.

New Inventions

WARNING DEVICE FOR INTRAVENOUS THERAPY

THE introduction of plastic burettes for intravenous infusion therapy has simplified the provision of devices to give warning of incipient emptying of the container.[1]

With rigid bottles the weight of the liquid has been the parameter which has been measured,[2] but with a soft plastic bag it is possible to sense the pressure at a point in the bag, and therefore obtain an indication of the hydrostatic head of fluid remaining. An extremely simple device can be constructed to perform this operation (see figure). The bag is located on a metal strip by two spring clips. Also mounted on the strip is a micro-switch (Burgess CRW 2), with its lever adjusted to be in line with the two clips. When the bag is sufficiently full the pressure exerted by the fluid on the lever maintains it in the depressed position; in the example shown in the figure the switch is released if the bag contains less than 15 ml. One set of contacts in the switch is made when the lever is depressed, another when it is released, making it possible to operate an alarm or warning system which, as a precaution against possible hazard caused by accidental spilling of saline or other fluids, should be of a low-voltage battery-operated type.



The warning device.

The volume at which the switch operates can be varied by positioning the switch further up or down the brass strip.

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1. Farquhar, J. W., Shannon, D. W., Batchelor, A. D. R. *Lancet*, Sept. 2, 1961, p. 537.
2. Shoenfeld, M. R., Edis, M. A. *ibid*. 1960, ii, 851.

THE LANCET

LONDON 2 SEPTEMBER 1961

Has Mankind a Future?

HAS mankind a future? This grim question can hardly fail to suggest itself to anyone with sufficient imagination, and a long enough memory, who reads the presidential address this week to the British Association. Speaking on the Humanity of Man, Sir WILFRID LE GROS CLARK outlined the salient features of human evolution up till now. The most recent anthropological discoveries, he said, trace mankind back to hominid ancestors who lived half a million or even a million years ago. Though their brains were little larger than those of a gorilla, there is evidence that they used tools, and they probably had the beginnings of speech. But it took hundreds of thousands of years of struggle with the elements, wild animals, and disease before their descendants, about ten thousand years ago, founded civilisation by forming relatively stable communities in which cooperation became more necessary. And civilisation took about the same proportion of its own span to achieve the cardinal features of our present epoch—the internal-combustion engine, flying, and radioactivity. Today, because of this accelerating acceleration of knowledge, and of the power it brings, the question is whether the civilisation which man has slowly and laboriously built can avoid disastrous dissolution, and whether our species can escape at least partial extinction by "the misapplication of its own ingenuity".

The factor that, in Sir WILFRID'S view, determined the evolution of man, and the gradual development of an integrated society, was consciously directed cooperativeness; and a broad historical trend is evident towards progressive unification of mankind:

"But the basic difficulty with the larger groupings of human society . . . is that, with increasing population pressure, the altruistic sentiments which in the course of a long evolutionary history have become ingrained in the mentality of the *individual* are too apt to be suppressed by the narrow interests of each particular *group* . . . we now have to face the seemingly paradoxical fact that the larger the units of cooperation in social communities the greater the tendency for their segregation into populations opposed to each other by conflicting economic and ideological interests. Thus the historical process of unification has tended to slow up and ultimately threatens to come to a halt. If it has sometimes been the outcome of conflict in the past this can no longer be envisaged as practicable in the future, for a major conflict involving the nations of the world today must lead to a degree of destruction that would render precarious the very existence of mankind."

What is so alarming is that, though this is recognised by all who are familiar with the facts, people in general continue to behave as though it were not true; and few ask—publicly at any rate—whether there is no better alternative than to oppose threats with threats, and, if need be, force with force, with the appalling implications of such a course of action. They seem content that the game should be played in the old impulsive way, though the stakes are now quite different. For nations to change their pattern of behaviour may be extraordinarily difficult, but it is plainly necessary; for even the most traditional actions may now be highly irresponsible in view of their all too probable consequences. To say that the handling of international relations sometimes appears irrational and atavistic is not to belittle the complexity of the problem but rather to underline it. What seems to us important is that more people should challenge the assumption that there is nothing else to be done. That is surely the essential preliminary to finding a better way.

In a broadcast the other day, Mr. JOHN RAE [1] said that his experience as a schoolmaster has taught him that we are the victims of myths about war, and that our children are still being indoctrinated with false ideas about its nobility. "The nuclear bomb," he said, "has given us time to think . . . We could start by teaching all those children who look to us for guidance that killing is a weakness and an evil that man must learn to outgrow." In his address LE GROS CLARK rightly emphasised the part played by science in promoting a view of life in which frontiers are relatively unimportant. Our task, he said, "is to inculcate as widely as possible that spirit of freedom in scientific enquiry which gives full expression to the deep-rooted altruism which . . . is an essential attribute of the humanity of man". Prof. JOHN COHEN [2] has lately suggested a "Human Pugwash"—a regular international meeting of men and women concerned with the human sciences. All such international human contacts are helpful, and it is encouraging that they have become so much easier even during the last ten years.

But perhaps what is needed as much as anything at the moment (in all countries, if this were possible) is a little of the spirit of scepticism, to question some of our own certainties, so that our outlook may be both wider and longer—less parochial in place and time. When we are inclined to fulminate against some present enemy, we should remember what we have said in the past about our present allies—even, indeed, as recently as twenty years ago. And when we condemn dictatorships as incompatible with human values, we might recall that the Greek civilisation, from which we trace our democratic ideas, was built on slavery, and that, though Renaissance Florence or Elizabethan England may have been nurseries of freedom, they were far from giving it a safe childhood. Some forms of human society are more advanced and better than others; but none are wholly good or wholly bad, and the one certainty is *change*.

1. *Listener*, Aug. 17, 1961.
2. See *Guardian*, Aug. 22, 1961.

In the Cold War much of the effort of the two opposing groups goes into undermining each other's positions. Perhaps nothing short of disaster will stop this activity, for which so many apparently excellent reasons can be found on both sides. But to people who feel that mankind has other things to do, it may seem that a practical first step towards restoring normal human relations would be a truce to aggressive propaganda. If this could be agreed, even for a year or two, there might be a chance for both sides to think again. If we cannot have cooperation, then we must have competition; but, with a pause for tempers to cool, it should not be beyond human wit to ensure that this is economic rather than military, money being diverted from armaments to sustain a straightforward battle for economic supremacy. East and West alike, each side is sincerely convinced that it can offer a better way of life than the other; and both should be willing to put this conviction to the test in the hitherto uncommitted countries of Africa and Asia, which stand to gain so greatly from such a battle for their favour. We repeat some words written a few years ago [3]:

"If by curbing our fears and restraining our threats we can avert a conflict which will ruin both worlds, the two different civilisations may be able to live side by side and eventually absorb what is best in each other. On a historical view such coalescence of rival groups is very far from being impossible; and its attainment must be the aim of all who recognise that, for survival, all men must come to regard themselves as members of a single group . . ."

The Madras Experiment

FIVE years ago a series of controlled chemotherapy investigations began in Madras, where a Tuberculosis Chemotherapy Centre was established under the joint auspices of the Indian Council of Medical Research, the Madras State Government, the World Health Organisation, and the Medical Research Council of Great Britain. This has already produced results of great importance for all countries of the world in the treatment and control of tuberculosis.

The first objective was to find out whether patients with pulmonary tuberculosis could be treated as effectively and safely in their own homes as in hospital. It was found that chemotherapy with *p*-aminosalicylic acid (P.A.S.) and isoniazid was, in fact, as effective in malnourished Indian patients treated in their poor, overcrowded homes by an efficient team of doctors, nurses, and social workers as it was in similar patients treated in good hospitals.[4] Moreover, observations in the first year of treatment showed that the close family contacts of those treated at home were at no special risk compared with those in hospital.[5] These observations have now been extended for a further year.[6] The conclusions are unaltered. The main risk to relatives and others living, cooking, and feeding with tuberculous patients arises from exposure before the diagnosis is made: after diagnosis, and with well-managed chemotherapy, the risk is small and much the same whether or not the patient is removed from the home. In the first year active tuberculosis developed in 9 (3·5%) of 256 contacts of patients treated at home and 18 (6·6%) of 274 contacts of patients treated in hospital. In the second year, during which all patients were at home, there were 3 (1·9%) further cases among contacts of those treated throughout in their homes and 4 (2·4%) among contacts of those treated initially in hospital. But all these 7 cases arose among contacts tuberculin-positive at the first examination—that is to say, among those already infected when the patient started treatment. In the second year no cases appeared in either group among those who had been uninfected initially.

The implications of this study of contacts go beyond the problem of treating patients at home in the underdeveloped countries where hospital beds are far too few. The results do, indeed, provide public-health support for widespread development of outpatient treatment in such countries. But they should also lead to reconsideration of the policy of strict segregation of tuberculous patients under treatment in the more favoured countries, with a view to reducing the psychological harm and economic loss that this can entail. But traditional beliefs are difficult to change; and it may be as difficult to modify the tradition of segregation as it apparently is to learn the other great lesson of the Madras experiment—that tuberculosis can be treated effectively by chemotherapy alone, even when patients continue hard manual work and remain undernourished. Rest and good food may be pleasant for the patient; but they are not necessary for his recovery.

The studies on chemotherapy have been carried further by a neatly planned investigation of the effects of treatment beyond a year.[7] After a year's chemotherapy with P.A.S. and isoniazid, 130 of the original 163 patients were classed by stringent criteria as having "quiescent" disease. 126 of these were allocated at random to one of two groups: one group (65 patients) received 150–200 mg. of isoniazid alone for the second year; the other (61 patients) an inert tablet. At the end of the year, 61 patients in the isoniazid group still had "quiescent" disease, and 60 of these were again allocated to one of two treatment groups—30 continued isoniazid and 30 received an inert tablet. Various comparisons were possible by this experimental design. At the end of the third year there was, in fact, little difference between any of the groups. 6 (10%) of the 61 patients who received only one year's treatment relapsed bacteriologically, compared with 3 (5%) of the 65 who received two or three years' treatment. There were no relapses in the third year in either the group who continued treatment with isoniazid or the group who did not. DAVADATTA et al.[4] concluded from their detailed analysis that there was no evidence that a second or third year of treatment with

3. *Lancet*, 1954, i, 815.
4. Tuberculosis Chemotherapy Centre, Madras. *Bull. Wld Hlth Org.* 1959 **21**, 51.
5. Andrews, R. H., Devadatta, S., Fox, W., Radhakrishna, S., Ramakrishnan, C. V., Velu, S. *ibid.* 1960, **23**, 463.
6. Ramakrishnan, C. V., Andrews, R. H., Devadatta, S., Fox, W., Radhakrishna, S., Somasundaram, P. R., Velu, S. *ibid.* 1961, **24**, 129.
7. Devadatta, S., Andrews, R. H., Angel, J. H., Bhatia, A. L., Fox, W., Janardhanam, B., Radhakrishna, S., Ramakrishnan, C. V., Subbaiah, T. V., Velu, S. *ibid.* p. 149.

isoniazid alone, after a year's treatment with isoniazid and P.A.S., gave better results than careful observation during those years and prompt further chemotherapy when a relapse was detected. This is yet another important fact for the planning of large-scale treatment; and it could lead to considerable saving of money and trained staff where both are scarce.

Concurrently with these primary investigations of the value and safety of home treatment, the Tuberculosis Chemotherapy Centre has studied the effects of treatment with isoniazid alone.[8] This form of chemotherapy has the attractions of economy and apparent simplicity. Four regimens were studied: 10 g. of P.A.S. and 200 mg. of isoniazid in two equal doses daily, 200 mg. of isoniazid in two doses, 400 mg. isoniazid in two doses, and 400 mg. in a single daily dose. The results were clear-cut. All the regimens of isoniazid alone produced poorer results than isoniazid and P.A.S., and the best was a single daily dose of 400 mg. At the end of a year, 90% of patients who had received P.A.S. and isoniazid had negative cultures, compared with only 76% of those who had received a single daily dose of isoniazid, 59% of those who had received 200 mg. twice daily, and 51% of those who had received 100 mg. twice daily. This superiority of the higher dosage of isoniazid is interesting. It differs from the findings of another investigation in which the Medical Research Council has taken part—the study in East Africa. There, treatment with a much larger daily dose of isoniazid (about 10 mg. per kg. body-weight twice daily, compared with about 9 mg. per kg. once daily in India) gave results only slightly better than 100 mg. isoniazid twice daily (about 2·2 mg. per kg. twice daily).[9] Both reports point out, however, that the large doses of pyridoxine given to the patients in East Africa to reduce the toxic effects of the high dosage of isoniazid may have interfered with the antituberculous activity of the isoniazid, there being some experimental support for this possibility.[10]

Another point of practical importance in assessing the value of particular regimens for large-scale treatment was the finding that the large cachets in which P.A.S. and isoniazid were prescribed were no less acceptable to the patients than the small tablets of isoniazid, and that two doses of this drug a day were no less acceptable than one. This finding, like all the others in these Madras investigations, must, of course, be related to the conditions of the experiment. Although the patients were treated in their homes and had to be relied on to take the drugs as prescribed, there was a highly efficient system of supervision by a generously staffed clinic. With less skill, less supervision, and less staff, results might be poorer, and patients might have taken little tablets once a day more regularly than big cachets twice a day.

The finding that a single dose of isoniazid daily gave better results than half the same dose given twice daily also has important implications. Very little is known about the relation of rhythm of dosage of antituberculous drugs to results. Almost universally streptomycin is administered in a single daily dose; yet other drugs continue to be given twice or three times a day. Possibly this may to some extent be attributed to the tradition of giving drugs in relation to meal-times. Too little attention has been paid to the size of the individual dose of antituberculous drugs, as opposed to the total daily dose. There is scope for much further investigation of the subject. It seems likely, however, that the apparent superiority of a single dose of isoniazid and the attraction to the patient (which may be spurious) of a single daily act of medicine-taking may lead to increased use of this regimen in the future, now that isoniazid with thiacetazone (both in relatively small doses) seems to be an acceptable substitute for isoniazid with P.A.S.[11]

The Madras workers have not neglected the further treatment of patients in whom the initial treatment with isoniazid and P.A.S. or isoniazid alone has failed. Some of these have been treated with streptomycin and pyrazinamide,[12] and the results have been encouraging. With 1 g. of streptomycin daily on six days a week (the injection being given at the clinic) and 1–1·5 g. of pyrazinamide in a single daily dose by mouth, 32 (56%) of the 57 patients who began treatment attained bacteriological quiescence by the end of a year. During the year 18 had the chemotherapy changed owing to persisting bacteriological positivity. No toxicity to pyrazinamide was observed; but in 18 the dosage of streptomycin was reduced because of possible toxic manifestations.

The major endeavour of the Madras investigation has been to study the practical problems of chemotherapy in the field—that is, in the social and environmental conditions in the community—in order to find the most effective practicable drug regimen and treatment organisation. But many other valuable results have been obtained in other directions. For example, detailed bacteriological investigations by Indian and British workers have shown that isoniazid-sensitive tubercle bacilli isolated from patients in South India are on average less virulent than bacilli from British patients, when the virulence tests are done by intramuscular injection in guineapigs,[13] thus confirming earlier work in India.[14 15] This difference in virulence is not apparent when guineapigs or mice are infected intravenously.[16]

The fruitfulness of the Madras investigations can be traced to able planning and conscientious execution. We can be proud of the participation of the Medical Research Council of Great Britain in such a model of international cooperative research; and we must hope that nothing will be allowed to prevent the Madras experiment from continuing its valuable progress.

8. Tuberculosis Chemotherapy Centre, Madras. *ibid.* 1960, **23,** 535.
9. East African/British Medical Research Council Isoniazid Investigation. *Tubercle, Lond.* 1960, **41,** 83. See *Lancet,* 1960, i, 1013.
10. McCune, R., Deuschle, K., McDermott, W. *Amer. Rev. Tuberc.* 1957, **76,** 1100.
11. East African and British Medical Research Council Thiacetazone/Diphenylthiourea Investigation. *Tubercle, Lond.* 1960, **41,** 399.
12. Velu, S., Andrews, R. H., Angel, J. H., Devadatta, S., Fox, W., Jacob, P. G., Nair, C. N., Ramakrishnan, C. V. *ibid.* 1961, **42,** 136.
13. Mitchison, D. A., Wallace, J. G., Bhatia, A. L., Selkon, J. B., Subbaiah, T. V., Lancaster, M. C. *ibid.* 1960, **41,** 1.
14. Frimodt-Møller, J., Mathew, K. T., Barton, R. M. *in* Proceedings of the Thirteenth Tuberculosis Workers' Conference; p. 157. Tuberculosis Association of India, New Delhi, 1956.
15. Frimodt-Møller, J. Technical Report of the Scientific Advisory Board; p. 153. Indian Council of Medical Research, New Delhi, 1957.
16. Wallace, H. G., Mitchison, D. A., Rees, R. J. W., Bhatia, A. L., Gangadharam, P. R. J. *Tubercle, Lond.* 1961, **42,** 212.

Annotations

EXAMINERS FOR NURSING

IN all forms of vocational training is is difficult to strike even an uneasy balance between theory and practice, judging accurately how much theory the student should be offered and at what point in his curriculum. In nursing, as in medicine, the difficulty has been aggravated by the rapid accumulation of new and complex methods, techniques, drugs, and devices; and the General Nursing Council have lately recommended some changes in the traditional pattern of medical and surgical lectures offered to the student nurse. Instead of a course in medicine and another on surgery given at an arbitrary point of the nurse's training, perhaps unrelated to her practical experience, the Council recommend that an elementary course on both medicine and surgery should be given somewhere about the end of her first year, and a more specialised course about the end of her second year, which would integrate the different specialties and point the application of different nursing procedures.

In a letter describing these recommendations (p. 551) Miss Margaret Louden, F.R.C.S., says that they will be reflected in the changes which the Council are introducing into the written part of their final examination. Instead of three papers (on nursing, nursing applied to medicine, and nursing applied to surgery) there are to be two general papers which will be corrected by a panel of nurses and doctors; and Miss Louden, who is chairman of the Council's board of examiners, asks some of her colleagues to volunteer for this task. In the past the medical examiners have usually been consultant physicians or surgeons; but, as the papers are in future to be more general, the Council would now be glad to have the help of other doctors who are interested in the training of nurses. Miss Louden suggests that these might usefully include some of the medical critics who in recent years, sometimes in our own columns, have suggested that the Council's examinations have been "too academic". She believes that such criticisms are not always well informed, and that most nurses are "quite able" to answer the criticised questions. Some medical doubters may still feel uncertain as to how many girls the questions may have deterred from sitting the examination, but they will have no doubt as to the answer which doctors should give to a request for help from a profession on which they so greatly depend.

FARMER'S LUNG

THE difficulty of defining a clinical syndrome in terms of pathology is seldom more evident than in the condition known as farmer's lung. The syndrome was first described by Campbell [1] in 1932. It consists of fever, malaise, cough, tightness in the chest with dyspnœa, sometimes cyanosis, and occasionally hæmoptysis. It usually occurs in farm workers after repeated exposure to the dust of mouldy hay or straw. Examination may reveal crepitations at the lung bases, and diffuse reticulonodular shadowing may be seen radiographically. Specimens of lung tissue may show granulomatous inflammation of the interstitial tissues resulting in fibrosis and emphysema.

Campbell's original account concerned 5 farm workers in Cumberland. Fawcitt [2] reported further cases from Cumberland and some from Westmorland also. Törnell [3] described a similar condition in Sweden, and Sweeney [4] found cases in north-west Ireland. Fuller [5] reported a series of 32 cases from Devonshire, and Williams and Mulhall [6] 10 cases from Radnor and North Breconshire. In the U.S.A. Frank [7] reported 27 cases and Dickie and Rankin [8] 32 cases, in 8 of which lung biopsy was undertaken.

All these reports largely accord with each other in their description of the syndrome. There is less agreement as to the cause of the pathological changes and the clinical picture. Fawcitt, for example, regarded it as a "bronchomycosis", while Törnell concluded that it was a moniliasis. Others, such as Williams and Mulhall, have suggested that it is due partly to choking of the terminal bronchioles by hay dust loaded with spores. Frank believed it was due to an initial pulmonary response to inhaled organic dusts followed by sensitisation to such dusts and to the spores they contain. Dickie and Ranken thought that it was possibly due to a hypersensitivity response to moulds or their products. Two further papers on the subject have appeared.

From Houston in Texas, Jackson and Yow [9] have reported 2 cases of "pulmonary infiltration with eosinophilia" with the subtitle "report on two cases of farmer's lung". 1 patient was a housewife who worked in a hayloft, the other was a farm-equipment salesman. Both had illnesses not dissimilar to farmer's lung; but in the 1st there was pronounced eosinophilia, and penicillium and aspergillus species were repeatedly isolated, and in the 2nd also there was eosinophilia (no report on culture for fungi is included). In both, corticosteroid therapy was followed by a striking response. In this country eosinophilia has not commonly been found in farmer's lung: in one unpublished series of 12 cases there was no instance of eosinophilia. Nor would the contention by the Houston workers that sometimes farmer's lung resembles Löffler's syndrome,[10] because in it there is a triad of pulmonary infiltration, eosinophilia, and a benign clinical course, command universal agreement. On the contrary most workers insist that, unless the patient is removed from the dust hazard, repeated attacks may leave him with lungs damaged by emphysema and fibrosis. The clinical picture described by Jackson and Yow resembles pulmonary aspergillosis much more closely than farmer's lung. Their article is valuable in demonstrating the difficulty in distinguishing between these two, possibly overlapping, conditions.

In the second paper Staines and Forman [11] report the results of a postal inquiry conducted on behalf of the research organisation of the College of General Practitioners. General practitioners and consultants reported to them 444 cases, forming a larger series than any previously described. The criteria for diagnosis were a history of exposure to fungus-contaminated vegetable dust, a cough, and dyspnœa with abnormal chest signs in the absence of obvious other pulmonary disease. It is therefore quite possible that conditions other than farmer's lung were included. This work again emphasises the difficulty of exact diagnosis.

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2. Fawcitt, R. *Brit. J. Radiol.* 1936, **9**, 172.
3. Törnell, E. *Acta med. scand.* 1946, **125**, 191.
4. Sweeney, P. J. *Ulster med. J.* 1952, **21**, 150.
5. Fuller, C. J. *Thorax*, 1953, **8**, 59.
6. Williams, D. I., Mulhall, P. P. *Brit. med. J.* 1956, ii, 216.
7. Frank, R. C. *Amer. J. Roentgenol.* 1958, **79**, 189.
8. Dickie, H. A., Rankin, J. *J. Amer. med. Ass.* 1958, **167**, 1069.
9. Jackson, D., Yow, E. *New Engl. J. Med.* 1961, **264**, 1271.
10. Löffler, W. *Beitr.Klin. Tuberk.* 1932, **79**, 338, 368, 566.
11. Staines, F. H., Forman, J. A. S. *J. Coll. gen. Practit.* 1961, **4**, 351.

Both these recent papers point to the need for detailed work if the picture is to be further clarified. One valuable contribution is that of Williams,[12] who has found in patients with farmer's lung, firstly, that the aspergillin skin test was negative and, secondly, that whereas an extract of fibre from mouldy hay (but not fresh hay) produced a distinct reaction, the inhalation of an extract of mixed aspergillus, penicillium, and monilia spores did not. This suggests that the noxious agent is not the fungi themselves but the hay or straw, altered by the fungi or the heat the fungi generate.

CAMP HYGIENE

No sooner had our ancestors shut themselves within walled cities for safety and commercial advantage than they began to build pleasaunces in the country outside where they might escape the crowds, the noise, and the smell of their fellows. The habit spread; but now paid holidays, the five-day week, the motor-car, and a self-indulgent prosperity have thrown the countryside open to the common man, and what began as " the English weekend " is the rule throughout Western Europe. The elderly, the infirm, or the merely rich may stay at hotels; but almost as many choose an al-fresco holiday in a tent or caravan. To many a farmer whose land lies by the sea, caravans are the most remunerative crop of all, and the effect of the cult of the body brown (or lobster coloured) on the economy of the Mediterranean countries must be considerable.

There was a time when the camper came and went as he listed with (perhaps) verbal permission from the landowner. One camper made no difference, and three were a source of income; but thirty-three are liable to be a social and sanitary nuisance. Oddly enough, many campers genuinely prefer the company of other campers. The caravan, being more conspicuous and less mobile than the tent, called attention to the need for some control of the simple life, and now in most countries there are regulations intended to preserve the health and enjoyment of the refugees from the cities. The Council of Europe has published a report on the hygiene of camping sites which compares the regulations in force in the member countries and makes some suggestions for greater uniformity.[13]

It recognises that the young man with a tent on the carrier of his bicycle does not ask for the same luxuries as the family in a caravan who intend to outspan for a week or two. Camp sites should be classified by their amenities (cf. *Le Guide Michelin*), but 2000 inmates are enough anywhere. 30 litres (say 5 gallons) of water per head per day is recommended as a minimum supply for all purposes, and a separate nonpotable supply for washing is very properly discouraged. The drinking-water should be tested for purity twice a year (this to our way of thinking is quite insufficient). The suggested proportion of washbasins (10%), shower-baths (3%), and closets (3%) seem to us to be, like the water-supply, a bit on the low side. There are some sensible ideas on concentrating toilet and washing facilities (for persons and pans) for better conservancy. In the long run the disposal of waste is the biggest hygienic problem in every camp, and it cannot be neglected because the campers are on holiday. Medical attention (including tetanus antitoxin and anti-venin) should be available in emergency. In all but the smallest camps there should be a full-time warden. Before any camp site is inaugurated the plans must be approved by the local health authority, which will supervise the hygiene of the camp as long as it is open.

Existing local regulations differ from these suggestions only in detail. In the Netherlands and Scandinavia alcoholic drink may not be sold in camps. In some camps there are letter-boxes, telephones, and places where cars may be washed. Some camps hire out air-mattresses (and offer facilities for their speedy inflation) and provide sockets for electric razors. Some provide football fields. It all seems a long way from " Scouting for Boys ". In this country it is not usually the temporary camp used for holidays—though some of these are fairly sordid—which worries the medical officer of health, but the permanent caravan colony initiated with or without permission from the planning authority.[14] The usual excuse for their existence is that the inmates cannot get houses, but we suspect that cheapness and the relative absence of domestic responsibility are attractive to many. The standards suggested in this report are below those desirable in a permanent colony, but if every site conformed to them the health authorities would have less cause for worry.

ROLE OF RETINAL PIGMENT

IT is well known that in fish, amphibia, and birds, as well as in some invertebrates with compound eyes, the pigment of the retinal pigment epithelium moves to cover at least some of the receptors in response to illumination of the eye. It has been generally assumed[15 16] that this movement of pigment, which in teleost fish and some amphibia is accompanied by appropriate movements of the rods and cones, is a device whereby the sensitive rods are protected from undue stimulation by bright light in the absence of a pronounced pupil response. The idea that pigment migration is associated with adaptation has been strengthened by the work of two Swedish physiologists—Bernhard and Ottoson.[17 18] They constructed dark-adaptation curves for diurnal and nocturnal lepidoptera, using the size of the electroretinogram as their criterion of sensitivity. In the nocturnal species they found that the dark-adaptation curve was in two parts and that the second increase of sensitivity, which was not present in diurnal species, was associated with retraction of retinal pigment uncovering the rhabdomeres of the retinula cells.

In many vertebrate eyes in which there is no evidence of pigment migration in response to light and dark, the epithelial pigment is, nevertheless, extremely prominent. This is particularly true of pure-cone eyes. In the only completely diurnal mammalian family known to have pure-cone retinæ—the squirrels—the processes of the pigment-epithelium cells are long and filled with pigment, and these processes envelop the outer segments of the visual cells.[19 20] Tansley has found that this is also true of the geckos, both diurnal[21] and nocturnal[22]; but the noc-

12. Williams, J. V. Personal communication.
13. Camping Hygiene. Council of Europe: Committee of Experts on Public Health. Strasbourg. 1961. Pp. 74.
14. See *Lancet*, July 8, 1961, p. 110.
15. Garten, S. *in* Graefe-Saemisch Handbuch der gesamten Augenheilkunde; vol. 3, ch. 12, p. 13. Leipzig, 1908.
16. Walls, G. L. *Cranbrook Inst. Sci. Bull.* 1942, **19**, 146.
17. Bernhard, C. G., Ottoson, D. *J. gen. Physiol.* 1960, **44**, 195, 205.
18. Bernhard, C. G., Ottoson, D. *Acta physiol. scand.* 1961, **52**, 99.
19. Arden, G. B., Tansley, K. *J. Physiol.* 1955, **127**, 592.
20. Arden, G. B., Tansley, K. *ibid.* 1955, **130**, 225.
21. Tansley, K. *Pfluger's Arch. ges. Physiol.* 1960, **272**, 262.
22. Tansley, K. *ibid.* 1959, **268**, 213.

turnal species are thought to have evolved from pure-cone diurnal ancestors and to have retained many of their ocular characteristics. In pure-cone species there is no pigment movement in response to illumination changes; and the retinal pigment must, therefore, have another function not concerned with adaptation. One of the most striking features of pure-cone eyes is the way in which each individual visual cell is separated from its neighbours by a dense mantle of pigment. It has been believed that the function of this pigment may be to ensure the optical isolation of each individual receptor, thereby improving the fineness of the " grain " of the retina and so increasing visual acuity. Until now this has been only a surmise, based largely on the fact that, except in nocturnal geckos, it is always cones—the receptors associated with good visual acuity—that are so isolated, while rods are usually left unseparated. Now we have some more direct evidence, once again from work on invertebrates.

In the first issue of a new international journal, *Vision Research*,[9] Kalmus [10] describes an investigation into the visual acuity of two species of fly—the housefly, *Musca domestica*, and the seaweed fly, *Cœlopa frigida*. In both species he was able to examine both the common wild type with pigmented eyes and a white-eyed mutant with unpigmented eyes. He tested the optomotor reactions of all four types, and by this means found that the visual acuity of the unpigmented mutants was greatly reduced. In the housefly, visual acuity in the white-eyed type was less than a twelfth of that of the normal; while the white-eyed individuals of the seaweed fly showed hardly any optomotor response at all.

Thus the pigment of both vertebrate and invertebrate eyes can apparently have a double role. Where pigment migration in response to light and dark is a feature, especially in the absence of an active pupil, the retinal pigment seems to protect the sensitive rod cells from too much stimulation. Where a retina is specifically developed to provide an overall high acuity, as in the tree and ground squirrels and in the diurnal reptiles, the pigment aids this function by optically isolating each receptor from its neighbours.

THE CIRCLE OF WILLIS

ALTHOUGH Thomas Willis first described his arterial " circle " at the base of the brain three centuries ago, our understanding of this anastomosis is still incomplete. It takes the form originally described in only 52% of people [11]; and zones of supply may, it seems, vary even in response to movements of the head and neck.[12 13] In post-natal life the final vascular pattern develops by elaboration of certain channels and disappearance of others from a primitive embryonic plexus. Padget [14] described the early appearance of anterior and posterior divisions of the carotid artery. The anterior gave rise to anterior and middle cerebral arteries with a large embryonic olfactory branch which later atrophied, an optic branch, and a median branch running in the midline over the corpus cellosum. The normal adult branches of this division may fail to develop; and then the other embryonic vessels, normally absent or inconspicuous, are large. The posterior division of the carotid artery persists as the posterior communicating and posterior cerebral arteries. A stapedial branch of the petrous portion of the carotid artery retains connection with the ophthalmic artery and links up also with middle meningeal branches, thus forming an anastomosis between internal and external carotid systems. From the cavernous portion of the carotid artery a temporary branch runs to the basilar artery. Occasionally this artery persists into adult life.[15] Berk [16] reported 6 cases of anomalies of the circle of Willis which could be explained in such embryological terms, demonstrated the deficient and anomalous vessels by angiography, and analysed the abnormal anatomy.

Such considerations can be of practical importance. One significant feature is the variable consequences of occlusion of a main artery: Brain [17] emphasised the importance of congenital anomalies of the circle of Willis in cerebral softening. Such anomalies are also important when perfusion of the brain is contemplated, whether for administration of cytotoxic drugs [18] or for deep hypothermia. If the perfusion is applied through certain selected vessels the volume of brain served in this way depends on the integrity of the anastomosis. Alpers et al.[11] found that, besides absence of some vessels, string-like vessels might be found with a diameter of less than 0·1 mm.; and in 22% of cases a posterior communicating artery was deficient to this degree. This means that perfusion of the carotid arteries alone may not provide sufficient circulation for the vertebral distribution; cooling of the whole brain has been found to follow perfusion of one carotid artery, [19 20] but this may not apply to all subjects.

Kuhn [21] obtained simultaneous angiography of carotid and vertebral arteries by cannulating the right brachial artery. The dye was injected to fill the brachial, subclavian, and innominate arteries as far proximally as the arch of the aorta. It was then carried on by arterial pressure into the right carotid and vertebral arteries. A rapid film-changing device enabled the circle of Willis to be displayed under the conditions that obtain with normal blood-flow. The posterior communicating artery was seen only rarely, and then as a slender filament. Blood distribution in the posterior part of the circle of Willis and its branches was bilateral, in contrast to the ipsilateral flow described in animals.[22] Collateral circulation from one side to the other was demonstrated by contralateral carotid compression, and was commonly found to be defective. Communication between carotid and vertebral circulations was also variable.

Localised perfusion of the brain is still an experimental procedure. Before it can be applied clinically some method will have to be found of overcoming the variability of anastomosis. Perfusion of both carotid arteries and the larger of the two vertebral arteries would probably suffice, but the vertebral arteries cannot always be perfused successfully.

9. *Vision Research*, 1961, **1**, nos. 1 and 2, June, 1961. Published by Pergamon Press, Oxford. Libraries, &c., £10, individuals £3 10*s*., per annum. In United Kingdom papers should be submitted to Prof. Arnold Sorsby, F.R.C.S., Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2.
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13. *ibid.* 1961, **24**, 95.
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Special Articles

EQUIPMENT FOR INTRAVENOUS FLUID THERAPY OF CHILDREN *

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THE equipment widely used in parenteral fluid therapy has been designed very largely for adult patients. For children changes in design are necessary; and the recent appearance of new sterile-packed, disposable giving-sets

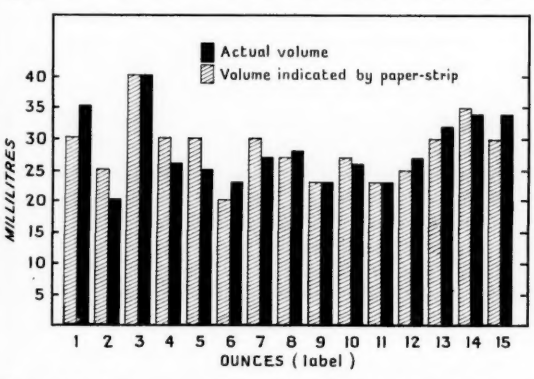

Fig. 1—Actual volume compared with volumes indicated by graduated paper labels on M.R.C. type of bottle.

provides an opportunity for making suggestions for the guidance of manufacturers. The principal needs are a means of measuring the volume of fluid given over short time-intervals, some device for preventing accidental overloading of the infant's circulation, and a method for controlling accurately the flow-rate of fluid. These must be combined with sterility, and with simplicity of design which reduces cost.

MEASUREMENT OF VOLUME

By Graduated Bottle

Until recent years the bottle has been the only routine method of measuring volume. The standard M.R.C. "narrow-waist" bottle is marked only at 180 and 540 ml., and these graduations are effective only when the bottle is standing on its base. For detailed measurement graduated strips of paper are usually stuck to its side; but, because of the bottle's irregular shape, they are not readily positioned with accuracy. In some hospitals straight bottles of uniform diameter are in use for certain fluids, and different graduated strips exist for these. Such strips may be graduated in either the imperial or metric system. The use of an incompatible strip and bottle leads to inaccuracy and possible danger.

This was demonstrated (fig. 1) by allowing 1 fl. oz. as indicated by a properly applied paper-strip to run from an M.R.C. type bottle. The actual volume was then measured in a cylinder and compared with the reading on another strip graduated in millilitres. 1 fl. oz. seldom proved to be 28 ml., nor did the ml. graduation strip and the actual volume compare closely.

All the usual solutions are in fact commercially available in good-quality glass bottles graduated quite accurately at 50 ml. intervals in such a way that the fluid level falls past the clearly legible 100, 200, 300, and 400 ml. marks. (Others in existence are intended to be read by an inverted observer with a gift for doing subtraction sums.) Fig. 2 represents a simple experiment with such a bottle.

1 fl. oz. at a time, measured by the paper-strip available for the hospital's standard "narrow-waist" bottle, was drained and measured in a cylinder. The true volume varied widely, indicating that such graduated strips are unsuitable for use on bottles other than those for which they are designed. The delivered volume corresponded closely to the millilitre reading on the bottle itself until just before the bottle emptied.

The recent introduction of disposable plastic bags of parenteral fluids entirely deprives the pædiatrician of this method of measurement.

By Rigid or Collapsible Burette

Rigid.—Volume can be measured very accurately by introducing a sterile glass burette into the system below the bottle and above or below the drip-chamber (Fletcher 1951, Rickham 1959). That there is a demand for such equipment is indicated by the commercial production in this country of a sterile disposable recipient set with a rigid plastic burette for infants. This will be favoured by those who believe that a difference of even a few millilitres from the prescribed hourly dose is important. This disposable set has the advantage over the glass burette of convenience and possible economy. Unlike the collapsible variety, however (see below), such burettes require an air intake into both the bottle and the burette. When the burette has been filled and the fluid column above it interrupted by the application of a clamp (fig. 3), the baby is safe from sudden accidental fluid overdosage. But should the burette empty, the infusion will stop and only the cotton-wool filter in the burette air inlet offers any sort of barrier to the passage of air into the baby. This

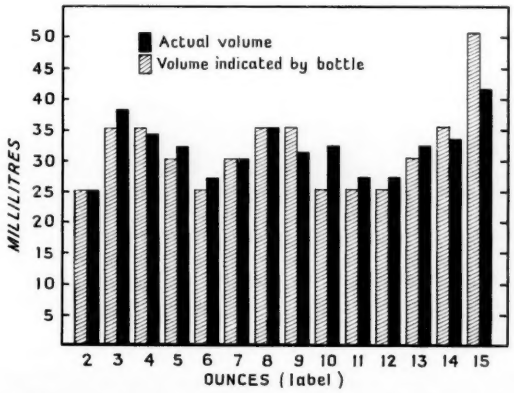

Fig. 2—Actual volume compared with volume indicated by graduations on straight glass bottle.

* The substance of a report prepared by a subcommittee of the Clinical Staff of the Royal Edinburgh Hospital for Sick Children.

danger is slight in a well-organised and adequately staffed neonatal unit, but equipment must necessarily be designed for safe use in a busy emergency hospital at night when close nursing supervision is unavailable.

Collapsible.—At least two types of collapsible plastic disposable burettes are widely used in North America. They are filled from the bottle, and the fluid column above them is then interrupted by a clamp. The contents of the burette empties by gravity, and atmospheric pressure collapses the burette so that no direct air intake is necessary.

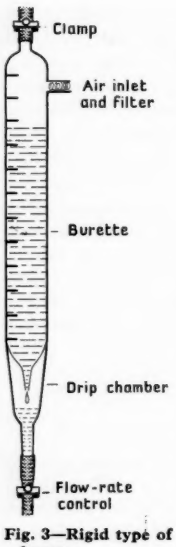

Fig. 3—Rigid type of burette.

The first type consists of a number of plastic sachets, each of which holds 10 ml., joined in series (fig. 4). In theory the content of the burette is 10 ml. × the number of sachets, and the application of a clamp at an appropriate point between the sachets permits any multiple of 10 ml. to drain. It must be used with a conventional giving-set, and its introduction into the system is associated with a small risk of contamination. The burette should provide a very convenient means of measuring volume; but, in practice, the weight of the fluid column tends to overdistend the lowest sachet while the uppermost one underfills.

The other type (fig. 5) is a plastic bag (graduated at 10 ml. intervals) which is an integral part of a giving-set. In practice accurate measurement may be a little difficult as opinion on the level of fluid may vary. The error in either burette is not critical, but, if the burettes fail to measure accurately, then they fail in one of their main objectives and are simply efficient safety devices (see below) of unnecessarily complicated design. In both types complete emptying of the burette, although free from the risk of air embolism, will result in stoppage of the infusion with possible loss of further use of the vein.

Fig. 4

Fig. 4—Variable filling of compartments of collapsible plastic burette because of hydrostatic pressure.

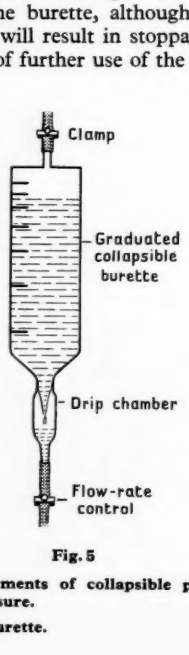

Fig. 5

Fig. 5—Bag-type collapsible plastic burette.

To prevent this the nurse is likely to refill the burette before it empties, and in the multiple-sachet type she will find it impossible to decide how much of the burette's original content the infant received. Again the error is small, but the accuracy of measurement is no greater than can be obtained with the graduated bottle alone.

CONTROL OF FLOW-RATE

The flow-rate of an intravenous infusion can be controlled in part only by the equipment, owing to the variability of such intracorporeal factors as venous pressure and venospasm. Intravenous equipment for use in infancy should embody the best means of controlling flow-rate and of preventing sudden fluid overloading should one of the intracorporeal factors alter.

The tubing itself should be of a consistency which resists collapse on slight bending but allows easy compression by the controlling mechanism. Its bore may also be important, and the flow-control clip must be efficient at slow rates. Control on the disposable set currently issued at this hospital is inadequate for infants and needs reinforcing by some such device as a metal gate-clip over a piece of split rubber tubing which in turn surrounds the plastic tube.

PREVENTION OF OVERLOADING

Both the collapsible plastic burettes described will prevent both accidental overloading with fluid and air embolism. Some such device is essential for venoclysis in infancy and should be part of a giving-set which is supplied assembled and sterile. It need only be a simple bag of approximately 100 ml. volume (accuracy is unnecessary), because the accidental entrance of that volume of fluid is unlikely to be lethal, and a smaller burette may have to be refilled too often. As a safety device it does not require graduations, and this fact, together with the simplest possible design, should mean reduced cost.

Interruption of the infusion because of unobserved premature emptying of the bag can easily be prevented by a simple, durable, and cheap electric device which can "feel" the plastic bag and trigger a visual or auditory alarm when approximately 15 ml. is left (Simpson 1961).

INJECTION POINT, NEEDLES, CANNULÆ, AND DRESSINGS

The giving-set should include one point at which the tubing is suitable for the injection of drugs. The giving-sets currently supplied to this hospital include needles which are quite unsuitable for use in small children. New pædiatric sets should have neither attached needles nor cannulæ; but a selection of these, separately packed, should be available. Nylon catheters, with Luer fittings, which can be boiled or autoclaved, are very suitable, and others of relatively cheap "boilable polyethylene" may become available.

Small transparent dressings, permeable to water-vapour, through which the drip incision may be inspected would have some advantages. Both polyethylene and nylon sheeting have been used for this purpose; but convenient, commercially produced, sterile dressings are not yet available.

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RESETTLEMENT UNIT IN A MENTAL HOSPITAL

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OVER the past years the number of admissions and discharges at mental hospitals has increased steadily and the patient's average duration of stay has shortened. Less encouraging is the fact that once a patient has been in hospital for more than two years, his chances of discharge are relatively small. In the third year of his stay they are 1 in 14, falling to 1 in 86 after ten years, and 1 in 196 after twenty-five years (Brown 1960). Despite a welcome redirection of interest from the recent admission to the chronic patient, efforts to help long-stay patients to leave hospital and to continue working in the community remain spasmodic and haphazard.

The long-stay patient is a disabled person with three main handicaps: (1) his disturbance of motivation or slowness or residual thought disorder; (2) his attitude to his illness, to work, or to discharge from hospital; (3) the social response of employers, relatives and society, to his illness, and his lack of references or belongings. These disabilities, caused respectively by illness, personal attitudes, and social circumstances, vary in relative importance from case to case, but they must all to some extent be overcome if the patient is to be resettled.

The patient has to begin to overcome them, and rediscover the use of his residual capacities, within the social structure of the mental hospital. According to Goffman (1957) the mental hospital is a "total institution":

> It places a barrier between the patient and the outside world; it subjects him to a diffuse and restrictive authority in every sphere of his daily life, and his opportunities for personal responsibility are limited. There is a split between patients and staff, reinforced by hostile stereotyped impressions on both sides. Work is often done slowly and without a sense of purpose. The patient loses status as a family member or as the member of an occupational group, while he is slowly, but relentlessly stripped of identity, personal belongings, money, a work record, and a reference.

It is difficult to imagine the work of rehabilitation going forward in such a social setting. It can only take place if small units are set up within the mental hospital where the social effects of the total institution can be lessened (Jones and Rapoport 1955) and an attempt made to reduce disabilities, change attitudes, and enable the patient to make full use of what residual capacity remains. A resettlement unit of this kind was started at Netherne Hospital in April, 1957. It is not the only ward in the hospital from which patients are being resettled, but the arrangements in it are particularly suitable for difficult placement problems.

OUR UNIT

The unit was established in a large villa built about 50 years ago, which was adapted, with little structural change, to house about 40 men and 50 women patients. All patients have been continuously in hospital for at least two years, are under 55 years of age, are doing some form of work, and are "stabilised" in the sense that their symptoms are not disturbing to themselves or others. 2 men and 2 women nurses work in two shifts. A psychiatrist works on the unit part-time and a psychiatric social worker (P.S.W.) full-time. An assistant matron and an assistant chief male nurse attend staff meetings and are a link with the nursing administration. A male and a female occupational therapist are a link with the patients' work situation. A disablement resettlement officer (D.R.O.) from the local labour exchange attends the weekly assessment conference. A social psychologist was engaged on research for the first two years (Folkard 1960a and b).

ASSESSMENT OF THE PATIENT

Before rehabilitation begins, the patient's disablement and residual capacity, and attitudes and fitness for resettlement, are reassessed.

An up-to-date social history is made and at a case conference attended by all the staff the psychiatrist summarises the patient's illness and treatment, the nursing staff report on his social functioning and attitudes, and the occupational therapists describe his work. In the light of these reports the D.R.O. discusses possibilities of employment, and the P.S.W. chances of social resettlement. The patient himself is invited to the meeting to express his plans and wishes for the future.

Thus the staff are given information about every aspect of the patient's behaviour and come to see him from the point of view of the family and the potential employer. In this way they obtain practical experience in patient assessment. Unrealistic anticipations, which all at one time or another hold out for this or that patient, are sensibly checked, while anxious caution, which might hold a patient too long in hospital, is relaxed. The reliability of these assessments will only be confirmed by the results of our follow-up, but the immediate benefits to the patient and to the agencies helping in his resettlement, in particular to the D.R.O., seem undeniable.

PREPARATION FOR RESETTLEMENT

The treatment of the patient's primary illness by present methods cannot always be fully effective; and he must therefore often have to adapt himself to work and his environment despite his disabilities. The activities of our unit are therefore planned to prepare him for life outside the hospital and to mitigate the disabling features of institutional life.

At present nearly 50 patients leave the unit daily from 6.15 A.M. onwards to work and earn in the community. Since it was started 60 have attended the local industrial rehabilitation unit (I.R.U.) while continuing to live in the hospital (tables I and II). In this and other ways the barrier between the hospital and the outside world is being broken down. The barrier is not only physical, for even when wards are unlocked and parole freely granted, patients may still be isolated from the community by lack of money, confidence, and suitable clothing.

Staff-patient Split

It is impossible to demolish entirely the authority structure of the institution, even in a semi-autonomous unit, but by repeated discussions and conscious effort on the part of the hospital administration and the staff many minor and some major restrictions can be overcome. Attendance at meetings or at social functions is not mandatory, friendships between men and women are viewed tolerantly and realistically, patients are paid by

the staff for whom they work and not on the ward. It is possible too that the free and frank communication between members of almost all grades of staff of both sexes in the staff meeting frees them to some extent from authoritarian pressures and modifies their attitudes towards patients.

We also make a deliberate effort to overcome the staff-patient split by holding weekly meetings of the staff and patients in small groups, and by a large monthly meeting of all the patients and staff. These meetings are held between 1 p.m. and 2 P.M., when the patients are in the ward and the staff from both shifts are on duty. The small groups have about 14 men and woman patients and are usually taken by two staff members. For example, an assistant matron takes a group with the male charge nurse, a male occupational therapist with a psychiatric social worker, a psychiatrist with a female student nurse, and so on. If they do no more, the meetings show the patients, week by week and month by month, our willingness to meet them regularly, and our respect for them and for each other in that we take part without regard for distinctions of rank. They give staff an opportunity to change their own attitudes as well as those of the patients. For the nurse it is a situation in which she can practise her interpersonal role, and handle groups (W.H.O. 1956).

Work

Patients who are going to be resettled must achieve regular habits of work as soon as possible. All patients who are not working outside hospital, work in a utility department, hospital service, or on industrial subcontract work.

They work on an average 5 hours a day; none do craft work, and none are retained as workers on the unit. This type of work situation not only prepares the patient, however inadequately, for the rigours of employment outside hospital, but gives an opportunity for a realistic assessment of his work capacity. It also gives him the chance to earn up to £1 a week; this acts as an incentive and enables him to achieve more independence and repair some of his personal losses. The work placement of every patient is determined solely by recommendations for his rehabilitation made by the resettlement conference, and not by the traditions or needs of the hospital. Hospital staff are often in this way deprived of " a good worker ", but they have accepted this change in policy with understanding.

Personal Responsibility

We expect patients to make their own beds, and to clean the ward and wash up on a rota. Men and women are allowed to mix freely, and their personal appearance and social behaviour improve. The acceptance of this situation by the hospital and the unit staff seems to reinforce responsible attitudes. The question of responsibility is freely discussed in the meetings, and the patients show by what they say and by their behaviour that they both understand and appreciate the situation.

Personal Losses

It is not realised how completely a long stay in a mental hospital " strips " a patient. He loses not only part of his identity and status, but self-confidence, initiative, money, and belongings. If he seeks employment, he lacks a work record and a reference. While he remains in hospital and until he starts earning, he cannot fully repair these losses. Some patients have families, private means or other help which makes reparation easier, but this is the exception.

Use of Drugs

These are some of the ways in which we try to prepare the patient for resettlement. Which are most important in lessening his disability or changing his attitudes we do not know. With some patients, they are successful; in others they achieve little. Though we rely chiefly on social forces as the means of preparing the patient, we do not eschew ataractic and other drugs where appropriate, but we do not believe that drug or other physical therapy alone is enough (Freudenberg et al. 1957). There seems little doubt, however, that the use of these drugs in psychiatry will increase the number of patients who will need the help of a resettlement unit.

RESETTLEMENT

For resettlement the hospital team needs the support of community services. It must be expanded to include the D.R.O., I.R.U., Government training centre (G.T.C.), employer, sheltered factory, hostel, and family or landlady. Adequate communication must be maintained with them all. It is important to see that almost all patients are registered as " disabled persons " and to take the full advantage of the Disabled Persons Act in placing them in work.

At first we allow the patient to work from the unit, going daily to his factory or other job. During this phase he pays the hospital for board and lodging according to a scale laid down by the Ministry of Health. We are fortunate in having possible jobs within easy reach of the hospital, and in a time of full employment we have not found many employers unwilling to engage a worker who is living in a mental hospital. This period gives the patient time to appreciate more fully the expectations of the world outside, to gain confidence, to repair his material losses, and consolidate his changed attitudes. During this time too, the family, the hospital, and the outside community change their attitude to him, seeing in his success at work the measure of his recovery. This is the first stage in combating his social handicap. From our point of view it enables us to make a final assessment of his capacity and stability.

Industrial Rehabilitation Unit

We encourage him to take a job which satisfies his inclinations, is at the highest level possible, and yet is within his limited capacity. It is often difficult to assess his capacity while he is still in hospital, since our work situation, realistic though it is, still falls short of the standards set by an employer. A period of reconditioning and vocational assessment at an I.R.U. is essential for many patients. The I.R.U. introduces them to the problems of industrial life under relatively sheltered conditions; time-keeping, travelling, and longer working hours. It also provides a work reference which the hospital unit cannot give. It changes his attitudes and gives him confidence (Wing and Giddens 1959). We have sent 60 patients to the Waddon I.R.U., and of 52 who completed the course 45 are in work though many are still living in hospital (table I).

This success-rate of 86% compares satisfactorily with the national figure of 56% for psychiatric patients (Jones 1956). 9 of these patients were accepted for vocational training at a Government training centre. Patients are usually found jobs by the D.R.O. through the labour exchange, but the P.S.W. has placed some. Some

TABLE I—RESULTS WITH 60 PATIENTS WHO ATTENDED I.R.U.

—	Men	Women
Completed course	35	17
Premature termination	5	3
Discharged and working	14	4
Working out—and resident in unit ..	15	12
Not working	5	3
Not traced	0	1

TABLE II—RESULTS OF 210 PATIENTS ADMITTED TO UNIT

—	Men	Women
Discharged	19 (22%)	25 (20%)
Readmitted (after up to six months' discharge)	0	6 (5%)
Transferred to other wards	27 (31%)	32 (25%)
Working out—living in unit	19 (23%)	29 (23%)
I.R.U. course	40 (47%)	20 (16%)

employers prefer the patient to come by himself for the interview, but it is sometimes helpful for the P.S.W. or nurse to accompany him if only as far as the factory gate.

If the patient loses his job a reappraisal must be made of his disability and the reasons for his failure before trying to find him another. This is possible only where information circulates freely and staff morale is high enough to face the inevitable disappointments and to try again. Where all the staff know the needs and difficulties of each patient, any member can deal quickly and confidently with problems as they arise.

Many patients who go to an I.R.U. are found on assessment to be far too disabled for work in open employment, but capable of work under sheltered conditions. The opportunities for this are still inadequate, but 6 of our patients have been found suitable jobs with Remploy Ltd., and 12 with the Ex-Services Mental Welfare Society (Thermega Ltd.)

Somewhere to Live

The patient is encouraged eventually to leave hospital and live in the community; but poor social acceptability or dependency may hinder this, as may a low-paid job. 19 men and 25 women have already left hospital (table II).

Of those discharged we know by follow-up that all except 3 are working. (2 are not in work and 1 cannot be traced.) Of the 6 women readmitted after more than six months outside hospital 4 are now working from the hospital and are included in that group. The average duration of these patients' last continous admission was seven years and many had had previous admissions to this and other hospitals.

Table III shows where the discharged patients are now living. Of the 6 women who were readmitted 4 were in living-in jobs, 1 in lodgings, and 1 in a hostel.

Brown (1959) has reported that patients who live in lodgings are less likely to return to hospital. The effect of

TABLE III—WHERE OUR 44 DISCHARGED PATIENTS ARE LIVING

—	Men	Women
Parental home	4	4
Conjugal home	1	2
With siblings	1	1
Lodgings	4	7
Hostel	6	2
Living-in job	3	8
Unknown	0	1

the " living group " to which the patient goes on discharge is complex, and Simmons and Freeman (1959) stress the need for the expectations of family members to match the patient's performance if resettlement is to be successful.

59 patients (table II) after review were assessed as unsuitable for resettlement, and they were returned to other wards and villas in the hospital. 10 were readmitted to the unit after an interval for a further attempt at resettlement. The positive aspect of this negative assessment should not be overlooked. There is no point in burdening the community rehabilitation services with patients who are too disabled for real hope of resettlement. Many such patients might in the future settle satisfactorily in a sheltered factory within the mental hospital.

CONCLUSION

The true benefits of our unit are difficult to assess, and discharge-rates are not the only, nor the best, criteria of success (Brown 1960). Resettlement is more than discharge; more even than the prevention of readmission. It aims to restore the patient to the most satisfactory life of which he is capable, despite his disabilities. When we consider the results of our first three years it is best perhaps to see them in terms of the opportunities we have been able to offer to our patients.

A resettlement unit can only flourish in a hospital where administrative change has already modified many aspects of mental hospital life and where one has the fullest cooperation of community services. It is a pleasure therefore to acknowledge our debt to Dr. R. K. Freudenberg, physician superintendent, for his part in promoting the administrative changes which made this unit possible; we also express our thanks to Mr. R. G. T. Giddens and the staff of Waddon industrial rehabilitation unit, to Mr. D. Pelton of Croydon labour exchange, and to other disablement resettlement officers. We have had the enthusiastic support of the nursing and occupational-therapy staff—in particular Miss D. B. Coombes and Mr. W. H. Rogers, who have done so much to make the scheme work. Dr. John Wing and Mr. George Brown have supported us with their interest and advice.

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Points of View

HELLENOMANIA—HELLENOPHOBIA

IT is not so long since the heyday of descriptive psychiatry, when the classifiers would create a disease from each symptom by rushing to their lexicons and fixing some more or less appropriate affix on to " mania " or " phobia ". (Some of their terms—kleptomania and claustrophobia for example—have passed into common use; but who remembers maieusiophobia, the " fear of childbirth ", or siderophobia, the " fear of railroad travelling " ?) Unfortunately, even now, the symptom of hellenomania, the Greek fury, is still prevalent among doctors; when we need a new word, we turn to the Greek. And Pappworth [1] says that about 3 new words a day are being added to Stedman's medical dictionary.

Of course, when a branch of learning expands, some new words have to be coined. What makes me unhappy is the rate at which they are pouring out, and the likelihood that some of the worst will survive with the good.[2] Moreover, many of them are jawbreakers or tongue-twisters, and many tell you nothing that could not be told by an English word or phrase understood by all who speak English.

To start with a simple, common example, hypokalæmia means " decreased plasma-potassium "; it tells us no more than that. There are several objections to its use: it is a new word to learn; it is easily confused with its opposite, hyperkalæmia; because any non-medical scientist will find it hard to understand, the sundering of science is increased; and if the Greek is translated literally,

1. Pappworth, M. H. *Lancet*, 1958, ii, 215.
2. Despite the hopes of the editor. *ibid.*

it means " decreased kalium (an invented word this, for potassium was one of the things the Greeks didn't have a word for) in the blood "—the *blood*, mark you, where the potassium content is enormously different from that in the *plasma* (which those who say " hypokalæmia " usually mean) or in the *serum* (which is what is actually measured).

The objection, of course, to the use of the English phrase is that life is too short for us to keep using three English words where one pseudo-Greek word will do; and it is true that hypokalæmia saves a lot of letters (though only two syllables). But this advantage diminishes when a whole bunch of minerals (electrolytes if you prefer that term, though electrolysis is probably far from your mind when you use it) are mentioned together, and the air is full of hyponatræmias and hypermagnesæmias, and heads are in a whirl. That poor overworked prefix " hypo " is nowadays being stuck on to all manner of words where " a- " or " an- " used to do very nicely, until someone got the idea that " a- " means " completely not " rather than simply " not ". I don't know what the Greeks would have thought of this idea, but it seems a pity to change a lot of comparatively simple words (and add a syllable to most of them) in the interests of dubious accuracy. Surely nobody used to think that analgesia invariably meant complete absence of pain? All the fuss seems a bit hollow to me, because when the hypo enthusiasts want to talk about an incomplete aplastic anæmia, they insist on " hypoplastic " but not on " hyponæmia "; you might think that, in patients with " hypoplastic anæmia ", the marrow is producing a little blood, but none of it is getting into the circulation. What is more, some of these enthusiasts lack the courage of their convictions, and talk of " partial and total hypoplasia "!

* * *

I'll admit that hypokalæmia is shorter to say and write than " decreased serum potassium "; but all too many Greek words are much longer than the English equivalent; they roll on sonorously, syllable after syllable. Ætiology means nothing more than cause, and atelectasis nothing more than collapse. Anamnesis is no longer much used for history, but immunologists still talk of anamnestic reactions. Symptomatology originally meant " the science of symptoms ", and might properly (if somewhat pompously) be used as the heading for a discussion of the symptoms of some disease; but its use has so degenerated that people say symptomatology when they simply mean symptoms. Asymptomatic is a confusing long word that may mean either " symptom-free ", when it is used of a patient, or " causing no symptoms ", when it is used of a disease: I suppose we must be thankful that hyposymptomatic is not yet in common use.

It is love of the ever-rolling syllable that makes many people prefer Greek; they use it not only in scientific articles, but in slang; " I didn't find any pathology " (lesion); " the patient was hæmorrhaging " (bleeding). And what on earth, save love of long words for their own sake, could make anyone coin such phrases as " cholecystokinetic intake " and " albuminocytologic dissociation "? The first refers to a meal that makes the gallbladder contract; it may be a little quicker to write, but the poor reader has to stop in his tracks and figure it out. The second refers to diseases where the protein content of the cerebrospinal fluid is increased out of proportion to the cell-count—or the other way round; I forget which, and the phrase does not help. Incidentally, I wonder how that word xanthochromic got attached to cerebrospinal fluid, and to nothing else. It means nothing more than yellow—or literally " yellow in colour " (as if it might be yellow in size or shape). I would say that " yellow in colour " is tautologous but there is a proverb about people in glass houses.

* * *

I am all for precision in language; but some of the crazes for precision have not been very soundly based and have done more harm than good. For some kinds of joint disease, arthritis may be a misnomer; but now that anyone who uses the word is liable to be pounced on, we have a proliferation of vague terms such as arthrosis, arthropathy (the hypertrophic pulmonary osteo variety is a fine example of a Greek jawbreaker), and arthralgia; and I once saw " arthralgia-like type pain ".

Idiopathic is a word that reformers have seized on. Originally it referred to a disease arising of itself, and the reformers believe, probably rightly, that no disease does this; so, they say, the word must be thrown out. But surely hardly anyone who uses the word nowadays means anything by it but " of unknown origin "; and the reformers have had to find a new word with just this meaning. The trouble is that they have hit on several, such as primary, essential, cryptogenic, and the very ugly agnogenic (you might well think this means caused by lambs; and will hypognogenic be invented for disease about which a little is known?). This suffix -genic (or -genous) is a particularly troublesome one, because it can mean " caused by " on one hand or " causing ", " giving rise to ", on the other. In the first sense we have agnogenic, psychogenic, and the fashionable iatrogenic; in the second atherogenic and osteogenic. One gathers that the " atherogenic index " is not an index that causes atheroma but is an index of atherogenesis; and that the confusion in the two uses of -genic has added to the confusion (and there is none more confounded) in the classification of bone tumours. Does an osteogenic sarcoma always produce bone, or does it simply arise in bone? No wonder some eminent pathologists prefer to speak of osteosarcoma. Hæmatogenous, however, means neither " causing blood " nor " caused by blood "; it means " borne by blood ".

* * *

One reason for using Greek for coining new words is that, since so many familiar medical terms are derived from Greek, we can often hazard a guess at what a new word means from our knowledge of its constituents as used in other words. This, though it has its dangers, is a real advantage: but often we are held up by the oddness of the word itself—it takes quite a bit of thought to realise that othæmatoma is not oth'æmatoma but ot'hæmatoma, a clot in the ear; similarly anosognosia may not at first suggest a'noso'gnosia, or ignorance of disease (a fascinating neurological symptom), and one might forgive those who, with vague memories of the French *oser*, think it means not knowing about daring, or those who, by analogy with the suffix in verbose, think it means not knowing much. One might also forgive those who think that anodontia means " teeth in the anus ", and I have even more sympathy with those who are tricked into thinking that agranulocytosis is a super-abundance of agranulocytes. Incidentally, -osis has three distinct meanings—an affliction, an excess, and simply " presence of "; a dermatosis is a disease of the skin, but a lymphocytosis is not a disease of lymphocytes.

Some purists object to the use of words whose parts are derived from more than one language, and call them barbarisms. I don't see any great harm in this, as long as the parts chosen are the most apt and euphonious that can be found whatever their derivation. Unhappily these principles are often not observed; surely roentgenogram and roentgenologic, each a mixture of German and Greek, are two of the ugliest and most cumbersome words in the language; I hope they will never cross the Atlantic. I suppose Röntgen should be honoured for his discovery, but he already has his name attached to the unit of ionising radiation. What is the objection to X ray for the ray, X-ray picture for the picture, and radiographic and radiological for the adjectives? If X-ray picture sounds too slangy, and radiogram has already been appropriated to describe a combination of radio and gramophone, and radiograph could be mistaken for the machine that takes the pictures (a logical use for that term, incidentally), why not return to the pleasant old word skiagram, a shadow picture? That is exactly what it is. I'm aware that the Americans use the " roentgen " affix to differentiate the use of X-rays from the use of radioactivity, but this is a somewhat artificial distinction when you are considering the picture produced—either kind of radiation can be used to make pictures.

* * *

I have various grouses against individual words culled from the Greek.

Thalassæmia (as has been pointed out by Sir Heneage Ogilvie) means " sea in the blood ". In one sense certain sturdy seafaring families have it; in another sense, we all have it, being descended from maritime creatures. Why not Cooley's disease, or Mediterranean anæmia, or hæmoglobin F disease, or target-cell disease?

Hemianop(s)ia, meaning " loss of half of the field of vision ", would not be too bad, but it has been turned into nonsense in the phrase " quadrantic hemianopia ".

Paresis has two very different meanings—partial paralysis, or general paralysis of the insane (dementia paralytica). Surely some term could be found less ambiguous than paresis and less cumbersome than the others.

Phenomenon is a good word to describe something truly phenomenal, but it is being degraded to mean anything observed. (It also has the disadvantage that its plural, phenomena, is often used as the singular. As a rule there is less confusion between singular and plural in Greek words—criteria is an exception—than in Latin words, where data, diverticula, and trabecula are as often as not misused.)

Parameter has precise meanings in crystallography, mathematics, and electrical engineering, and it seems to me to be a dreary and pompous medical fashion that uses it to mean anything that can be measured, or even observed.

Biopsy is fine for examining a specimen from a living person (it means the examination, not the operation to remove the specimen); and necropsy is fine for examining a dead person; but why on earth autopsy, which means looking at yourself?

A tetralogy is four related books or works of art, and I see no good reason why it should be applied to a collection of four related deformities reported by Fallot. This unique use of the word could well be dropped in favour of tetrad or syndrome or malformation.

Therapy seems a slightly pretentious way of saying treatment, but the only real disadvantage of it that I know is that patients sent to " Therapy " usually land in radiotherapy when they should be in physiotherapy, and vice versa.

Some appallingly cumbersome words can be replaced, with advantage, by a simple phrase: thus panhypopituitarism can be rendered by pituitary deficiency, and hypogammaglobulinæmia (ten syllables!) by gammaglobulin lack. Dysdiadochokinesis, on the other hand, is a word I would retain at all costs; it gives immense pleasure to the student who masters it, and it is the basis of at least one admirable limerick.

* * *

What makes people add to the burden of the doctor and the student by coining new words from Greek—usually the longer the better? I suppose that different coiners have different motives.

Some would remind us that Hippocrates was the father of our medicine, as the Greeks were the fathers of much of our science. Some believe that the use of Greek will aid communication between nations; but, even if he can understand the Greek words, the foreign reader will profit little if the context remains meaningless, as anyone will soon learn if he tries to read a textbook in some unfamiliar language: he will recognise the names of the arteries, but will not be able to tell whether they run medially or laterally—and their content will be not *hemos* but *blut* or *sang* or something equally meaningless to the Greek scholar. If we are to have a lingua-franca, it must cover the whole language and not a few peak terms.

Some of the coiners, I fear, have (consciously or not) the opposite intention—to increase the obscurity of their subject. Alongside the tendency in science today towards popularisation and explanation, there is another tendency to obscurantism, to making science appear a great mystery to be probed only by the initiated; and a specialised vocabulary is a great aid in this process. (Another popular aid is the use of abbreviations; the plastic surgeon who writes P.A.W.G. in the case-notes knows that not one person in a thousand who has not had training in plastic surgery will recognise that as " post-auricular Wolff graft ", and feels superior, like a member of an exclusive club, or a member of a schoolboy gang with a secret code.) Some coiners simply enjoy showing off; or enjoy the feeling of creation that goes with making two syllables stand where one stood before; or enjoy the rolling sound of such words as hypercholesterolæmia; or are caught in that parkinsonian vortex that makes work expand to fill the time available for its completion, expenses increase to absorb any rise in income, and words expand (in both length and number) to fill whatever paper remains to be written on.

* * *

Two very important words derived from the Greek are democracy and tyranny; the Greeks gave us the example of both, as well as the words. Words can be tyrants as much as men; and in a sense they are worse, for they are harder to slay. One of the chief horrors of *Nineteen Eightyfour* was the way in which language had been deliberately twisted to make it impossible for men to think straight any longer; they had then no hope of escaping dictatorship. We must use constant care to avoid any corruption of our language, anything that will weaken its strength and clarity. The needless proliferation of new and cumbersome words is a dangerous means of diluting and destroying language and with it thought; we must weigh carefully every candidate for admission to our tongue, and pounce on words that have lost their usefulness and on those which distort and emasculate the language. The flowing sound of Greek words is a siren song; let us not allow their richness to lead to our ruin.

D. M. JACKSON.

Needs and Beds

SURVEY OF A LONG-STAY MENTAL HOSPITAL POPULATION

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THE Ministry of Health's recent circular on future bed demand in mental hospitals forecasts a drop in the number of beds needed from the present figure of 3500 per million population to 1800 per million population in fifteen years' time. The statistical projection on which this estimate is based has been reported by Tooth and Brooke (1961).

The Ministry circular makes it clear that " these figures do not take account of the long-stay patients now in hospital ", but adds " where circumstances both inside the hospital and in the community are favourable, it has been demonstrated that many of these patients can be reclaimed and discharged. It is likely that their number will continue to decline, and *it is estimated that none will remain in sixteen years or a little more* ".

TABLE I—DISTRIBUTION OF PATIENTS BY LENGTH OF STAY

In hospital	Percentage	
	Males	Females
Less than 3 months	6·8	9·3
3 months–2 years	10·9	15·5
2–5 years	13·7	12·5
5–10 years	17·7	15·7
10–20 years	26·2	24·0
Over 20 years	24·7	23·0
Total	100·0	100·0

No figures have been adduced to support this assumption, on which the total estimate of future bed needs must in part depend. We are, therefore, reporting on a patient census carried out in a large mental hospital (Menston, Yorkshire), with particular reference to the nature of the long-stay population, and its potentialities for rehabilitation in the community.

By nature of its size (2350 beds), its relative shortage of medical and nursing staff, and its lack of occupational-therapeutic facilities, the hospital has been compelled to adopt in the main a custodial form of care. All mental hospitals do not face equally severe problems; but, if there is to be a decline in the number of mental hospital beds, it is precisely this type of hospital which should logically be emptied first.

METHODOLOGY

The patient census covered all patients in the hospital at one point in time, records being collected over several days and corrected to midnight on a certain night in June, 1959. Questionnaires were designed for easy recording, and kept as brief as possible, since long and complicated forms can create hostility, conscious or unconscious, in the person responsible for completing them, and this may invalidate results.

Questionnaires were completed by senior ward nursing staff, from records kept on the wards, at the request of one of us (C. P. G.), who checked much of the information personally.

TABLE II—AGE OF LONG-STAY PATIENTS AGAINST LENGTH OF TIME IN HOSPITAL

Percentage of long-stay group (777 males)

Males in hospital	75+	65–74	55–64	45–54	35–44	25–34	15–24	15–	—
5–10 years ..	0·64	2·32	4·76	5·02	7·85	4·89	0·26	..	..
10–20 years ..	1·29	4·12	7·85	10·04	11·58	3·35	..	..	..
Over 20 years	4·50	9·91	12·48	7·98	1·03	0·13	..	..	..
Total	6·43	16·35	25·09	23·04	20·46	8·37	0·26	..	100·00

Percentage of long-stay group (764 females)

Females in hospital	75+	65–74	55–64	45–54	35–44	25–34	15–24	15–	—
5–10 years ..	3·01	5·50	5·89	5·37	3·40	1·57	0·26	..	..
10–20 years ..	4·19	8·38	12·17	6·54	5·24	1·83	..	..	..
Over 20 years	9·95	10·99	10·34	4·19	1·18	..	..	..	..
Total	17·15	24·87	28·40	16·10	9·82	3·40	0·26	..	100·00

HOSPITAL POPULATION AS AT JUNE, 1959

The population on the census date was made up of 1133 men and 1218 women. These figures do not necessarily indicate the respective incidence of mental disorder for the sexes, but are simply determined by the accommodation available.

If those patients in hospital for two years or less are classified as short-stay, and those in hospital from two to five years as medium-stay, this leaves 68·6% of the men (777 patients) and 62·7% of the women (764 patients) in the long-stay group (table I). This is, in fact, an underestimate, since some patients who have at present been in hospital for shorter periods of time will, in fact, stay to join the long-stay group.

Table II shows clearly that all the long-stay patients in hospital are not elderly. Over three-quarters of the men (77·22%) and over half the women (57·98%) are under 65 years of age, and many of them still in their thirties and forties. On the basis of the General Register Office abridged life-table 1957–59, and assuming that the average life-span of a long-stay mental patient does not materially differ from that of the general community, it is calculated that a minimum of 651 of these 1541 patients would still be alive in sixteen years' time. This estimate, of course, leaves out of consideration the question of how fast this

TABLE III—OCCUPATION OF LONG-STAY PATIENTS IN HOSPITAL

Percentage of long-stay group (777 males)

Males in hospital	Ward dom. & O.T.	O.T. dept.	Utility work	Outside work	Total working	Total not working	—
5–10 years	12·36	2·96	2·83	..	18·15	7·59	..
10–20 years	19·18	2·57	7·08	..	28·83	9·40	..
Over 20 years	17·37	2·06	6·18	..	25·61	10·42	..
Total	48·91	7·59	16·09	..	72·59	27·41	100·00

Percentage of long-stay group (764 females)

Females in hospital	Ward dom. & O.T.	O.T. dept.	Utility work	Outside work	Total working	Total not working	—
5–10 years	11·52	2·35	2·36	0·13	16·36	8·64	..
10–20 years	19·37	2·62	3·40	..	25·39	12·96	..
Over 20 years	17·28	0·92	3·40	..	21·60	15·05	..
Total	48·17	5·89	9·16	0·13	63·35	36·65	100·00

1. " Ward dom. and O.T." refers to domestic cleaning on the wards and to occupational therapy undertaken on the wards, as opposed to occupational therapy undertaken in the Occupational Therapy Department (represented in the next column).
2. " Utility work " refers to cleaning, gardening, &c., undertaken within the hospital building or grounds for the purpose of hospital maintenance.
3. " Outside work " means work for an independent employer during the day, while the patient is still resident in the hospital.

TABLE IV—CIVIL STATE OF LONG-STAY PATIENTS

Percentage of long-stay group (777 males)

Males in hospital	Married	S.W.D.	Single	–
5–10 years	6·05	3·73	15·96	..
10–20 years	7·08	4·89	26·26	..
Over 20 years	6·69	2·83	26·51	..
Total	19·82	11·45	68·73	100·00

Percentage of long-stay group (764 females)

Females in hospital	Married	S.W.D.	Single	–
5–10 years	5·49	8·52	10·99	..
10–20 years	6·99	10·94	20·42	..
Over 20 years	6·67	5·24	24·74	..
Total	19·15	24·70	56·15	100·00

"S.W.D." = separated, widowed or divorced.

chronic population is replacing itself, since it is concerned only with patients in hospital now.

It is evident that this long-stay population is not going to be eliminated by death in the next few years. If they are to leave the mental hospital, some other accommodation must be found for them. Whether they can make a successful adjustment to living in the community (with their families, or in hostels) must depend on a number of factors: Are they capable of employment? Have they near relatives? Have their relatives kept in touch with them? Is the mental illness of a self-remitting type, or is it one in which progressive deterioration can be expected? We now present evidence on these points.

Table III indicates that nearly half the long-stay patients (48·91% of the males and 48·17% of the females) are only working on their own wards, and that a further large proportion (27·41% of the males and 36·65% of the females) are not even carrying out these minor and limited tasks. Whether the cause is inability to work, due to the severity of the illness, or lack of opportunity to work, due to the custodial system of organisation, it is clear that the overwhelming majority of patients in the long-stay group would not be capable of sustaining paid employment in the community, even in a time of full employment.

Table IV confirms in this context the evidence of Abel-Smith and Titmuss (1956) that mental hospitals, like general hospitals, have a heavy preponderance of single patients, and that the bed-occupation rates are much lower among the "ever-married", including separated, widowed, and divorced. In the present context, however, we are concerned with discovering the proportion of patients who would have a marriage partner to return to if they were discharged from hospital. It will be seen that it is less than one-fifth of the total for both men and women.

TABLE V—FREQUENCY OF VISITING

Percentage of long-stay group (777 males) visited

Males in hospital	Weekly	Monthly	Annually	Never	–
5–10 years	10·29	6·04	3·47	5·92	..
10–20 years	13·12	10·03	4·50	10·55	..
Over 20 years	6·17	8·10	5·53	16·28	..
Total	29·58	24·17	13·50	32·75	100·00

Percentage of long-stay group (764 females) visited

Females in hospital	Weekly	Monthly	Annually	Never	–
5–10 years	9·64	6·65	3·39	5·61	..
10–20 years	12·39	9·26	6·26	10·30	..
Over 20 years	6·00	8·60	7·30	14·60	..
Total	28·03	24·51	16·95	30·51	100·00

The figures in table V refer to any visitors. It will be seen that 32·75% of the men and 30·51% of the women never have a visitor of any kind; and if the last two vertical columns of the table are taken together, it is evident that nearly half the patients in each case have no more than an annual contact with the outside world. These patients clearly do not have families or friends who would be prepared to support them in the event of discharge.

The difficulties of assessing diagnosis satisfactorily have been well publicised (Pasamanick et al. 1959, Reid 1960).

We have, therefore, not attempted a detailed breakdown under this head, particularly since the diagnoses given on the ward records had been made by a variety of psychiatrists over a considerable period of time. Proceeding on the assumption that the schizophrenic states are generally identifiable, we have simply separated those patients suffering from conditions of a schizophrenic nature from all others.

In table VI "all other conditions", of course, includes a variety of conditions for which the prognosis may be poor; but the size of the schizophrenic group alone is sufficiently striking to demonstrate that, for the bulk of the long-stay patients, recovery is unlikely, and further deterioration in personality and social adjustment is likely to occur.

TABLE VI—DISTRIBUTION OF LONG-STAY PATIENTS BY DIAGNOSIS

Percentage of long-stay group (777 males)

Males in hospital	Schizophrenia	All other conditions	–
5–10 years	18·40	7·34	..
10–20 years	27·03	11·20	..
Over 20 years	25·61	10·42	..
Total	71·04	28·96	100·00

Percentage of long-stay group (764 females)

Females in hospital	Schizophrenia	All other conditions	–
5–10 years	12·56	12·44	..
10–20 years	23·30	15·05	..
Over 20 years	24·21	12·44	..
Total	60·07	39·93	100·00

In this, as in other mental hospitals, schizophrenia remains the central problem. Its ætiology is unknown, it cannot be prevented, and although modern methods of care may facilitate naturally occurring remissions, there is no reason to believe that they favourably affect the disease process itself. Rollin (1961) has drawn attention to the grave social consequences which may stem from a redistribution of such patients in the community, and pertinently points out that "a disease is no less chronic because its manifestations can and do continue outside as well as inside hospital".

SUMMARY

A hospital patient census has been described, and the characteristics of the long-stay patient group have been analysed.

Statistics given in tables I–VI indicate that the long-stay patient group is not predominantly elderly, and that over 40% of these patients can be expected to be alive in sixteen years' time. Hardly any are used to occupations of a type which would fit them for outside employment; few have marriage partners; half have virtually no contacts with the outside world; and over two-thirds are suffering from advanced schizophrenia.

The evidence suggests that, in this hospital at least, the Ministry's assumption that "none will remain in sixteen

years or a little more " is unlikely to be fulfilled. Though it is recognised that deductions formed from the study of a single mental hospital cannot necessarily be applied generally, the findings of this census indicate that much further study is essential before basic assumptions about the future of the present long-stay mental hospital population can be made.

We wish to record our appreciation of the cooperation received from the officers of the Leeds Regional Hospital Board, and the nursing staff of Menston Hospital. Without this cooperation the survey would not have been possible.

The views expressed in this paper are not in any way to be taken as representing the opinions of the Leeds Regional Hospital Board.

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Symposium

ASSESSMENT OF PAIN IN MAN AND ANIMALS

AN international symposium was held under the auspices of the Universities Federation for Animal Welfare (UFAW) at the Middlesex Hospital Medical School on July 26-28.

Nature of Pain

In his opening address, Sir RUSSELL BRAIN, who presided over the symposium, pointed out that other people's pains are an inference from their words, and to a lesser extent from their behaviour. The pain of animals, since they cannot tell us about it, is an even more remote inference. Nevertheless, because emotions are surely diencephalic in their neurological location, and the diencephalon is well developed in animals and birds, he himself had no doubt "that the interests and activities of animals are correlated with awareness and feelings in the same way as my own."

Dr. K. D. KEELE (London) traced the development of man's attitude to pain and the theories of the nature of pain.

Prof. C. A. KEELE (London) described the sensations aroused by chemical stimulation of the skin by the use of the blister-base technique. This suggested the possible stratification of receptors at different depths in the skin. He proposed the term " metæsthesia " to represent the range of sensation produced by stimulation below the intensity required to cause pain. Dr. ROBERT SMITH (London) presented evidence that pain production is related to the intensity of the stimulus and demonstrated the phenomenon of metæsthesia by potassium and polypeptide stimulation of the blister base. The discussion which followed raised the question of the relation between the terms protopathic sensation and metæsthesia.

Peripheral Mechanisms

Prof. J. A. B. GRAY (London) took the chair for the afternoon session, which dealt with peripheral mechanisms of pain. Dr. A. G. M. WEDDELL (Oxford) demonstrated the structure of the terminal nerve elements in the skin and emphasised the importance of correlating the appearances seen under the electron microscope with those seen under the light microscope.

Prof. Y. ZOTTERMAN (Stockholm), in a paper on the specificity of cutaneous afferent nerve-fibres, concluded that our skin contains functionally specific receptors connected through specific channels to the brain. We do not yet know what makes these naked endings specific and we have to continue the search for the basis of this specificity at the submicroscopical level.

Dr. A. IGGO (Edinburgh) discussed his work done on single C-fibres in the conduction of impulses initiated by chemical and physical noxious stimuli from viscera, muscle, and skin. He was followed by Prof. H. HENSEL (Marburg) who demonstrated by film the recording of afferent impulses in human cutaneous nerves in single-fibre studies carried out in his laboratory.

Dr. W. KOLL (Göttingen) described his work on the action of various pharmacological substances on nociceptive spinal reflexes. The action of morphine on nociceptive reflexes is not an unspecific " narcotic " action and differs from the action of anæsthetics.

The ensuing discussion dealt with the specificity of the peripheral mechanisms. It was still not known whether the nervous system could interpret information from units responding to more than one form of energy, or if all quality of sensation depended on units responding to one form.

Central Mechanisms

For a discussion on the central mechanisms of pain Prof. D. HILL (London) took the chair.

Dr. G. GORDON (Oxford) described the electrophysiological approach to study of central mechanisms of somatic sensation. Dr. D. R. BOWSHER (Liverpool) and Prof. D. ALBE-FESSARD (Paris) presented a joint paper entitled Patterns of Somatosensory Organisation within the Central Nervous System. They have concluded that there are only two basic types of somatic sensation, the discriminative and non-discriminative. Discriminative sensation travels by the lemniscal pathway and is relayed somatotopically via the thalamus to the cortex. The anatomy and function of the extralemniscal non-discriminative pathway is still to a large extent unknown. Diffuse activation of the whole intact cortex is apparently necessary for the conscious appreciation of pain.

Dr. P. W. NATHAN (London) described the phenomenon of pain traces left in the central nervous system. He gave details of the experimental reproduction of pain in the phantom limbs of amputees, identical with previous painful experiences involving the amputated limbs.

Mr. J. HANKINSON (Newcastle upon Tyne) dealt with the surgical aspects of the relief of pain and described the technique of coagulative destruction of intracerebral structures under the control of stereoscopic radiography.

In the subsequent discussion possible mechanisms involved in phantom pain and trace phenomena were proposed by Prof. G. L. SCHERRER (Paris) and Dr. J. KIDD (Liverpool). As an example, Dr. M. R. A. CHANCE (Birmingham) drew attention to the audiogenic seizures which occur in rodents when their escape mechanisms are withdrawn.

Assessment in Man

Prof. O. L. ZANGWILL presided over the meeting on assessment of pain in man.

Prof. H. K. BEECHER (Boston, Mass.) surveyed some working hypotheses and referred to work he is undertaking on the effects of drugs on high-level intellectual performance. He thought that experimentally induced pain experiments often gave data which could not be related to results obtained at the clinical level.

Dr. J. D. HARDY (New Haven, Conn.) reviewed the work of his group on the pain threshold and described the clinical value of this work both for measuring the pain intensity of disease processes as well as the analgesic effects of drugs.

Dr. R. W. HOUDE (New York), in an appraisal of pain and analgesic drugs, argued that the proponents of " pathological " and " experimental " pain could resolve their differences by realising that they were attempting to equate different forms of quantitative data. He suggested a type of data analysis involving the " ridit" unit which could provide a solution for these difficulties.

Dr. C. WILSON (Liverpool) delivered a paper on autosuggestion and the placebo response. He described the various factors at play in the clinical evaluation of drugs which tend to be ignored and which introduce bias even when so-called blind methods are being used.

In the discussion which followed, Dr. K. D. KEELE described the relation between pain sensitivity as measured by the pressure algometer and the clinical picture. There was a lengthy discussion on the importance of environmental factors influencing the pain experience. It was generally felt that, in spite of the difficulties of psychophysical correlation, further efforts were needed in this field.

Assessment in Animals

The final meetings dealt with the assessment of pain in animals and the practical applications towards minimising the suffering of animals used in research. Prof. C. A. KEELE took the chair.

Dr. D. D. BONNYCASTLE (Jersey City, N.J.) discussed the use of animals in assessment of the action of analgesic drugs and showed that when low-intensity thermal stimuli were applied it was possible to demonstrate the action of aspirin as well as morphine-like drugs. He emphasised the need for using small doses of drugs and for careful handling of the animals.

Dr. R. L. KITCHELL (Minnesota) described his work on the recording of electroencephalographic and reflex activities evoked by noxious stimuli in electrically stunned animals. He was trying to distinguish the psychic reaction (pain perception) in animals from activation of peripheral pain receptors (pain reception) with reflex accompaniments.

Dr. H. O. J. COLLIER (London) gave an account of his multiple toe-pinch test for assessment of analgesic drugs in guinea-pigs and rats. The responses to randomised applications of a light artery clip to all the toes provided more information than repeated applications to the same toe. The use of such correlated quantal variates saves animals and operating time. The method is useful for morphine-like drugs and local anæsthetics.

Dr. C. RADOUCO-THOMAS (Geneva) described his method, partly by means of a film, for electrical stimulation of dental pain in rabbits coupled with a technique for perfusing the roots of the incisor teeth. He could thus demonstrate the analgesic action of pethidine, its potentiation by perfused noradrenaline, and the antianalgesic action of reserpine.

Dr. K. SOEHRING (Hamburg) evaluated the methods used for testing local anæsthetic drugs before their introduction into clinical use.

Dr. J. JACOB (Paris) discussed the unconditioned and conditioned responses of mice in the hot-plate method used for testing analgesics. Morphine depresses conditioned more than unconditioned responses, and qualitatively it acts in a different manner on the two types of response.

The main point arising from this discussion was that in animals, as in man, sensitivity to noxious stimuli is influenced by environmental factors. In experimental studies on analgesic drugs stress should be avoided by careful handling of the animals, by allowing freedom of movement, and by the use of small stimuli and small doses of the drugs.

In the last session Dr. E. J. DELORME (speaking in place of Prof. A. Haddow) described several practical devices used at the Chester Beatty Research Institute to prevent discomfort in rats and other animals.

Major C. W. HUME pointed out that experiments ought to be done only by persons who have the requisite scientific training and can be relied on to avoid a wasteful infliction of discomfort. In order to prohibit experimentation by the incompetent it is necessary to have statutory powers such as exist in Great Britain, Sweden, Belgium, Denmark, and a number of other countries, but the cooperation of humane scientists is indispensable to work such a system. The British system may look preposterous on paper but it works well in practice. Where a humane tradition has been built up, a callous experimenter will be restrained by the opinion of his colleagues, and it is important that beginners in research should be taught a sense of responsibility towards all the animals which they use. The training of technicians is an important factor in the humane treatment of laboratory animals.

An important point was raised concerning the use of curare-like drugs to immobilise animals, after the effects of anæsthesia have worn off, in electrophysiological experiments on the central nervous system. Opinions were divided as to whether such experiments were justified, but many members felt that electrodes previously implanted under anæsthesia were preferable for both stimulation and recording. Such techniques can be used in conscious animals and provide a humane way of overcoming the complications introduced by drugs.

The proceedings of this symposium will be published in book form by UFAW, 7a, Lamb's Conduit Passage, London, W.C.1, early next year.

In England Now

A Running Commentary by Peripatetic Correspondents

Chairman of the appeal tribunal: Your name is John Smith?

Dr. Smith: It is.

Chairman: You are a doctor of medicine and a fellow of the Royal College of Physicians?

Dr. S: I am.

Chairman: You claim that you devote nine sessions per week to the appointment of consultant physician to the Wonderland Royal Infirmary?

Dr. S: I do.

Chairman: Do you acknowledge, Dr. Smith, that a third of the population is either under the age of 15 or over that of 65, and therefore outwith the orbit of a general physician?

Dr. S: I suppose . . .

Chairman: In your own interest, Dr. Smith, we can tolerate no suppositions here: we deal solely with facts. Surely these facts are common knowledge?

Dr. S: Well . . .

Chairman: Exactly; and you will not deny, I presume, that the cause of death in 36% of the people has its roots in the circulatory system, and that such disease is the province of the consultant cardiologist to the Royal Infirmary?

Dr. S: I cannot . . .

Chairman: Precisely; nor that, similarly, respiratory disease accounts for 13% of all deaths, this being within the purview of the consultant chest physician?

Dr. S: No . . .

Chairman: I am glad we agree, Dr. Smith. So it can hardly be denied that only about 18% of the population remains the concern of general physicians?

Dr. S: I doubt . . .

Chairman: Honest doubt, my dear Sir, is highly praiseworthy, but are we to question the evidence of the annual report of the Ministry of Health? I understand, Dr. Smith, that there is also a General Hospital in the precincts of Wonderland, and that the populace favours it at least equally with the Royal Infirmary?

Dr. S: I believe that . . .

Chairman: Quite so. The spirit in which you give your answers, Dr. Smith, is—if I may venture a comment—highly commendable. Among how many consultant physicians is the work at the Royal Infirmary divided?

Dr. S: Three . . .

Chairman: Three; and you being the most senior, will scarcely lay claim to more than a third of the load?

Dr. S: I would submit . . .

Chairman: Excellent; and of this resultant third of half of 18%, that is to say 3% of the medical work in the community served by the Wonderland hospitals, how much do you delegate to your juniors? Would a third be an overestimate?

Dr. S: Possibly . . .

Chairman: Possibly, as you say, it may be more, but we will not pursue the point. So it will be seen, then, that no more than 2% of all the work to be done falls to your lot, Dr. Smith. This, of course, leaves aside the whole of general surgery, orthopædic surgery, ophthalmology, venereology . . .

Dr. S: I give up!

Chairman: But you must not permit yourself to give up at this stage in our discussion, Dr. Smith. You have followed the successive development of our line of thought, and have seemingly not dissented at any stage of it: how then can you dissociate yourself from the inexorable logic of our mutual conclusion? This tribunal was asked to consider whether one session per week was a fair reflection of your true engagement. We consider that you have been most generously dealt with. You agree, gentlemen? Yes? Very well, then, the appeal is dismissed. Next case, please!

* * *

My fellow peripatetic's report on his rugged passage to rejection for a job recalled a much smoother path of many years ago which led to a surprise ending. I was flattered to be one of four on the short-list for a senior post, and it was agreeable to find that first-class travel and subsistence would be paid to attend an interview. All the candidates arrived early, and we agreed to lunch after the ordeal. I was most impressed by the Board of thirteen members who questioned me for half-an-hour about my career, opinions, and views as to how the post should be developed, staffed, and so on. It was all most courteous and thorough. As we sat at lunch in the club afterwards one of us spotted a friend sitting alone with a bottle of champagne. " He must be celebrating something, probably another addition to his family. I must congratulate him," he said. In a couple of minutes he returned with his friend bearing the bottle. " Dr. X. would like you all to drink his health, he's just got a very good job," he told us. "Well, actually I was appointed three weeks ago, but this is the first chance I had to get to the club," said Dr. X. At this point I decided I would never play poker with any of the other candidates, for not one gave the slightest sign of surprise when Dr. X. told us confidentially what post he had obtained. We smiled our congratulations and drank his champagne. After all, I don't suppose any of us *really* thought he would get the job for which we had been so solemnly yet farcically interviewed that morning.

* * *

On his first visit to London, David, aged 3, was impressed and terrified by the lions at the Zoo, and for the rest of the week his conversation was largely about lions. At the weekend, on another sightseeing tour, the lions at the base of Nelson's Column were pointed out to him. " Lions," said David's father, and David replied gravely, " Yes, Daddy, lions ". At each lion the same conversation took place. Then David's father pointed to Nelson at the top of his column. " Look, David," he said, " man," and David answered gravely once again, " Yes, Daddy, man ", and then added " frightened of lions ".

* * *

When the B.B.C. telephoned to say they wished to interview me about footwear and schoolgirls, a subject which I had mentioned in my annual report, I felt I should at least try everything once. My sound recording was duly passed by the archpriest in the neighbouring sound-proof room, but the television studio was a different affair altogether. The producer, with lightning speed, sized up the situation, selected the shoes —good and bad—to be shown and the X-ray photograph of the pronounced hallux valgus. By this time I had come to terms with my interviewer and realised that the B.B.C. resolved all subjects into three straightforward questions: What have you found? What is the significance of your finding? What are you going to do about it? All answers to beat 50 seconds. We had time only for one trial run before the count-down; meantime I had been advised not to wait too much for the interviewer but to go off more on my own. When the bell rang and the interviewer asked the first question, I went straight on down the course, scarcely giving him time to get in a word, and the poor producer and his cameramen were baffled to push the shoes and photograph on to the screen at the right time. When it was over we tiptoed silently away to make way for the next victim—a resourceful young woman doctor who had been climbing in Tibet.

My friends and staff were all very pleasant about it. Some said how well I had done and others said how interesting it was. My interviewer phoned a few days later, and I picked up courage and he told me, as I had suspected, that the producer had not been able to do his stuff at the right time. My interviewer, however, confessed—and he apologised for it—that he had asked the questions in the wrong order, and in my enthusiasm to obey the injunction to go ahead, I had not noticed. A week later I could refrain no longer from asking my secretary if she had seen it. " Yes," she said, non-committingly, " I was peeling the potatoes ". After further probing she added— " Not very good; they had the lights wrong on your glasses!"

Letters to the Editor

EUTHANASIA

SIR,—Dr. Colebrook was most kind in his remarks about the work at St. Joseph's Hospice, but there are a few comments I would like to make.

First, I would like to emphasise that excellent care of these patients has been carried out not only at St. Joseph's but also in other terminal homes and hospitals over many years. The research now being undertaken here under the department of pharmacology, St. Mary's Hospital Medical School, has been an attempt to develop the work and experience of many other people to whom we are most grateful. It began with analgesics only, but here more than in almost any other branch of medicine it is the whole person who has to be considered and helped. Controlled clinical trials are very difficult to carry out among this group of patients, but from the analysed records of several hundreds who have been cared for over the past three years we are now able to gain a much clearer picture of the most common problems and their solutions. We decided to employ established drugs so that eventually the methods of using them could more easily be suggested to doctors and nurses who care for these people in so many different situations. Detailed records, with tape-recorded conversations where possible, are kept of the patients' reactions and the results of the treatment. Information has been acquired not only about the use of drugs but also about the patients' own views of their illness and its significance. This has given some help in understanding their mental as well as their physical distress. We are now certain that we can approach this subject with confidence, and the rounds we are asked to arrange for medical and almoner students, for nurses, doctors, and ward sisters show that there is a great deal of concern about this problem. We shall be publishing reports of the work in due course.

Secondly, our aim is rather higher than just to render our patients " fairly comfortable ". We try, and we believe very often with success, to enable our patients to remain themselves throughout their illness, to find their own key to the situation and to use it. They make of it (consciously or unconsciously) not just a long defeat of living but a positive achievement of dying. This more than anything else gives courage to their relations and leaves something to be remembered with pride.

Our patients have a much higher incidence of pain and other symptoms than would be found in a random selection of people dying of cancer, because it is those who cannot be cared for at home who are sent to us. But all this can be controlled or greatly alleviated. We have done two years' work since *Care of the Dying* was written, and I have learnt a great deal during that time. We are now always able to control pain in terminal cancer in the patients sent to us and only very rarely indeed do we have to make them continually asleep in so doing. Most of our 60 patients at present are alert and able to enjoy their meals and their visitors; almost without exception they sleep through the night, many get up, and several go out either for weekends, for trips to other hospitals, or to the local park or pub.

I certainly agree with the writers previously quoted that there is much suffering among the dying in this country; but, without going into the reasons why I personally believe that euthanasia as advocated is wrong, I would like to emphasise again that it should be unnecessary and is an admission of defeat. We cannot take away the hard thing that is happening, and mental distress is far harder to help than physical; but the symptoms Dr. Colebrook describes can be relieved. We are not troubled with tolerance or addiction; patients are often on the same doses for weeks or months.

Finally, I would add that the " consolations of religion "

are as easily refused or disregarded at St. Joseph's as they are available. I am not a Roman Catholic myself, and nor are very many of our patients. All of them are visited by their own priests or ministers when they desire it, or by no-one if that is what they wish. We do not find that this is a problem but instead that we can cooperate and share fully in this side of the work.

Dr. Mullins makes an important point when she says that we would like to hear more from general practitioners and also from nurses about this subject. It is they who have the closest contact with people who are going through "terminal illnesses". Isolation is the greatest suffering these patients may have to bear. This applies to them both as a group left out of so much of our planning and as individuals who need a listener more than any other form of therapy.

St. Joseph's Hospice,
Mare Street,
Hackney, London, E.8. CICELY SAUNDERS.

SIR,—Ethics aside, it seems to me that each doctor *must* know where he stands if he is to hold his own against the firebrand advocates of killing. Life is our business, not death.

It is only because we believe this so strongly that we have struggled through the tangle of recent therapeutic advances to achieve success in many illnesses, fatal in the recent past.

Consider the havoc in the wake of an epidemic of untreated cerebrospinal fever (I have known wards full of demented and paralysed people). The impetus stemming from this type of experience stimulated the creation of sulphonamides.

When the medical scientist abandons "the ultimate good of man" as his goal—those who know nothing of God and His Kingdom will resort to killing.

It seems that our euthanasia advocates are unaware of the constantly changing attitudes of medical thought and creative ability—at present so rapidly in ascendancy. They fail to see that only by keeping our failures before our eyes can solutions be found.

The endless search for the happiness and life and survival of our patients is our destiny.

County Hospital,
Bantry,
Co. Cork, Eire. EUGENE F. MURPHY.

SIR,—I fully support your editorial (Aug. 12) questioning the value of euthanasia. This, however, is more than a sociomedical problem. It touches on one of the essential foundations of human society—the absence of the moral right to take the life of another. Justification for such untherapeutic therapy can rest only on a total lack of understanding of the nature and destiny of Man, and on the failure to question the ethical value of an action before deciding whether or not it should be performed.

Could there be any greater discouragement to the perfect practice of our profession than the widespread (as it must surely become) rejection of one of its most basic and traditional principles?

Belmont Hospital,
Sutton, Surrey. F. MAI.

ROAD ACCIDENTS

SIR,—That doctors should concern themselves with the prevention of road accidents is long overdue. No other people are quite so intimately concerned as we are with the terrible damage to the human body that can result from collision, with the expensive and painstaking repair of survivors, and with the social and psychological aftermath. It is a tribute to the therapeutic preoccupation of our services that the most careful thought doctors have so far given to this pandemic is the planning of better accident services. Prophylaxis, for some reason, is left to others, but unfortunately they are not very good at it. One is driven to despair by official road-safety campaigns of which the transparent virtue hardly compensates for their almost total uselessness. The existence, for example, of the Royal Society for the Prevention of Accidents lulls us into the false feeling that everything is well in hand; but apart from gathering useful facts, and publishing them, that body seems to depend on exhortation of the "Stop Accidents—Honour Your Code" variety. The alteration of people's attitudes—and still more of their habits—in things like this poses great problems and what little is so far known of current propaganda methods is not encouraging. No, it is the duty of the profession (and, in my view, of the Royal Society for the Prevention of Accidents, though it has so far not dared) to press for realistic legislation that goes well beyond breathalysers and other gadgetry.

There is much to learn from other countries—the U.S.A., for example, with more experience than us of high-speed driving, had a ceiling limit of 60 or 65 m.p.h. on every road of the five States I recently drove in, and I was told that this (or a lower limit) was universal. There is plenty of evidence that stricter speed limits here would cut accidents [1] and it is worth noting that a limit of 48 m.p.h. in Sweden earlier this year cut deaths by more than half.[2] But one fears that such proposals would be fought bitterly by the motor manufacturers and the Automobile Association—two bodies whose special interests in cars and motorists may sometimes impair their ability to act with appropriate urgency and determination. Another example: New York State has made it obligatory for cars to have attachments for front-seat safety-belts.[3] Vehicle construction is determined by appearance, speed, and economy—and, of course, safety; but only lately have the most elementary safety devices, such as padded dashboards, been seen on a few models. If disc brakes are so much safer, why are they not universal instead of just added to make fast cars faster still? Why should the four corners of the car not be made of pliable material, as on London newspaper vans? Or we might consider obliging the police to seal a governor set at 50 m.p.h. into the carburation of everything on wheels—as they used to in Calcutta a few years ago. The modern small car parallels better performance and deceptively good ride and cornering with lighter construction and less protection from chassis and bodywork. I believe (though I have not confirmed it) that one must comply with more public-health regulations in building a lavatory in the back garden than in mass producing a motor-car or motor-cycle. Action of course need not be entirely negative. A very large annual prize to the designer and manufacturer of the car, lorry, and motor-cycle causing the least percentage damage would be a fit project for one of the various motor millionaires.

My point is that we are still fiddling with this problem, despite awakening public conscience and recent legislation or attempts thereat (it is typical that a road safety Bill should be left halfway when Parliament rose—a motoring culture has long been reluctant to face severer motoring penalties.)[4] Nothing ever came of Margery Fry's bright idea of branding the cars of offending motorists, nor of Lord Mancroft's attempts to resurrect it a year ago.[5]). Finally, let any new measures be applied experimentally, so that we can tell what works and what does not. Road deaths should be the most accurate social indices we have, and if, say, a 55 m.p.h. limit in area A cuts fatal accidents compared with a matched area B, then we have some information worth having. I ought to pay tribute to the

1. See, for example, Preston, B. *Observer*, March 20, 1960.
2. *Times*, Jan. 11, 1961.
3. *Guardian*, March 20, 1961.
4. Wootton, B. Social Science and Social Pathology. London, 1959.
5. *Hansard*, April 26, 1960.

work of the Road Research Laboratory here: it seems to me that the only thing wrong with this excellent organisation is that no-one takes much notice of what it says.

Beckenham, Kent. RICHARD FOX.

MEDICINE AND HISTORY

SIR,—In his interesting paper (Aug. 26) Dr. Todd writes: "At the beginning of the 20th century the physician was almost as helpless to influence the course of diseases (except malaria) as were Hippocrates or Galen." Surely the therapeutic efforts of the physicians of sixty years ago are worthy of more praise? They had inherited many useful drugs and their understanding of the mechanism of disease processes was growing rapidly.

Paullitzky used ergot in obstetrics in 1787.

William Withering described the use of foxglove in dropsy in 1785. The drug was misused by some of Withering's contemporaries, and fell out of favour in this country. But it was reintroduced by Osler in the late 19th century.

Pasteur produced a vaccine against anthrax in 1881, and some time later developed a vaccine for treating hydrophobia.

In 1894 Roux prepared diphtheria antitoxin.

Of course these treatments had little effect on the morbidity statistics when compared with the advances of the next half-century; but at least some of the discoveries in the basic medical sciences were being put to use.

Arnold, Nottingham. TERRY COATES.

MANAGEMENT OF THIRD-STAGE COMPLICATIONS IN DOMICILIARY OBSTETRICS

SIR,—There are several very controversial statements in Dr. Fraser and Dr. Tatford's article (July 15).

Their reason for removing the patient to hospital is the supposed danger of domiciliary anæsthesia. They admit this must mean delay and a greater chance that the patient will become shocked, but claim that this can easily be treated by transfusion.

Is domiciliary anæsthesia dangerous? How many anæsthetic deaths have occurred in the past ten years in domiciliary obstetrics in unshocked patients? I should be surprised if this question can be answered today. Perhaps an investigation in the next few years might provide the answer.

Next they give a time of 15 minutes between receiving a call and arriving at the home. What matters is the time that elapses between the decision of the general practitioner or midwife to call the flying-squad and its arrival on the scene. In this town this time is often 30–40 minutes; and traffic is much heavier in South London.

The course to be followed by the general practitioner must depend on the circumstances. If the patient lives next door to the hospital, give ergometrine intravenously, summon an ambulance, warn the hospital, and send the patient there without delay. If the squad will take 30–40 minutes to arrive and a partner (or an anæsthetist) can be on the spot in 15 minutes, send for both the flying-squad and the partner. If when the partner arrives the patient is not in shock, anæsthetise with open ether or chloroform and remove the placenta manually.

In my opinion what matters is not the place where obstetric manipulations are carried out, but the skill and experience of the operator. If future general practitioners are properly trained, they will quite safely remove manually in domiciliary practice retained placentas in unshocked patients; and these patients will then require no transfusion with its accompanying risks. The present trend is apparently to teach that no obstetric operation can be done safely outside the walls of hospitals (notwithstanding the antibiotic-resistant staphylococci in them). I am sure such teaching is wrong and may occasionally lead to disaster.

I agree with them that certain of their cases should never have been booked for home confinement. But I would not include previous uncomplicated forceps delivery in this category.

Ipswich, Suffolk. IAN S. STADDON.

AUTOIMMUNE THYROIDITIS ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS

SIR,—The coexistence of systemic lupus erythematosus with goitre and evidence of thyroid autoimmunity has been reported by several authors.[1 2] We have had the opportunity to observe two patients with goitres who later developed S.L.E.

CASE 1.—A woman aged 28 (1956) had had a thyroid enlargement since the age of 18 which had increased in size considerably in the past few months. The goitre was diffuse and well marked on both sides of the neck. The patient was euthyroid; B.M.R., −2%. She complained of severe lassitude. The erythrocyte-sedimentation rate (Westergren) was raised to 85 mm. in the first hour, and the γ-globulin level was 3·2 g. per 100 ml. These results and a previous history of rheumatoid-like episodes suggested S.L.E. and a search for L.E. cells proved positive. Later the patient became febrile and developed a polyarthritis, symptoms of polyneuritis affecting the lower limbs, and pericarditis. Administration of prednisolone produced a rapid improvement in the general condition and the goitre became considerably smaller after three months' treatment.

In 1957 she became pregnant and stopped her treatment. In 1958 she was delivered of a baby weighing 2·5 kg. ($5^1/_2$ lb.) who died soon after birth. Postmortem examination revealed a congenital absence of the diaphragm. The thyroid gland showed large well-filled acini with an active epithelium and no signs of lymphoid infiltration. The patient was again treated with prednisolone and was also given thyroid extract. In 1959, thyroid antibody tests (kindly performed by Dr. D. Doniach) gave positive results: tanned red-cell agglutination (T.R.C.) titre 1/250,000; precipitin test negative; complement-fixation (C.F.) titre 1/5.

Soon afterwards the patient became pregnant again. Treatment was not interrupted this time and in May, 1960, she gave birth to a normal child weighing 2·5 kg. The mother's blood at that time showed a strongly positive nuclear fluorescence (A.N.F.) by the Coons technique, using sections of thyrotoxic thyroid gland as nuclear substrate. The thyroid-antibody tests were still strongly positive with a T.R.C. titre of 1/250,000 and C.F. titre 1/32 (thyroid microsomes). The cord blood gave serological reactions identical with those of the mother—i.e., A.N.F. +ve, C.F. +1/32, T.R.C. 1/250,000. On the fifth day after birth the baby's blood gave a positive L.E.-cell test while no L.E. cells could be demonstrated with the mother's blood. On the fortieth day, the baby's antibody titres had decreased considerably: C.T. +1/8, T.R.C. 1/2500, and at sixteen weeks all tests became negative. The mother's serum now showed positive thyroglobulin precipitins.

CASE 2.—A woman aged 34 (1960) had had thyrotoxicosis since 1954 and had been treated successfully with propylthiouracil. In May, 1960, she developed a bullous skin eruption around the ankles which healed up leaving circular scarred areas. Propylthiouracil was stopped at that time. In September, 1960, she developed pyrexia, arthralgias, severe lassitude, digestive symptoms, and a cough. She was given a ten-day course of chloramphenicol, 250 mg. t.d.s., and triamcinolone 4 mg. t.d.s. On this the temperature returned to normal but a blood-count showed leucopenia and agranulocytosis.

The patient was admitted with a diagnosis of drug sensitivity. She had an enlarged liver and spleen. Erythrocyte-sedimentation, 60 mm. in first hour; γ-globulins, 1·63 g. per 100 ml. Pyrexia varied between 103° and 104°. Tetracycline and prednisolone (50 mg. in twenty-four hours) reduced the

1. Doniach, D. Roitt, I. M., Hudson, R. V. *Rev. Mal. Foie*, 1959, **36**, 287.
2. White, R. G., Bass, B. H., Williams, E. *Lancet*, 1961, ii, 368.

temperature and the white-cell count gradually returned to normal. The general condition of the patient improved considerably. The thyroid presented a diffuse enlargement with a thrill and bruit over the gland. Basal metabolic rate, +18%; ^{131}I uptake, 100% at two hours, 100% at six hours, and 82·3% at twenty-four hours. Plasma-conversion ratio at twenty-four hours, 99·1%.

In view of the drug reactions, 8 mC of radioiodine was administered (Nov. 15, 1960) to achieve a permanent remission of the hyperthyroidism. The effects of this treatment were very unfavourable. The pyrexia and arthralgias returned, and a necrotic urticarial rash appeared. S.L.E. was now suspected, and prednisolone treatment was started again. In January, 1961, the basal metabolic rate was −17%; erythrocyte-sedimentation rate 36 mm. in first hour, γ-globulins, 1·96 g. per 100 ml., L.E.-cell test positive. Thyroid antibody tests showed a T.R.C. titre of over 2 million, C.F. titre 1/64. Immunofluorescent tests were positive, and showed specific staining of the thyroid colloid, cytoplasm, and nuclei (A.N.F.). At the end of January, the patient developed a characteristic facial butterfly rash. Rest in bed and prednisolone treatment led to clinical remission. The hepatosplenomegaly regressed and the body-weight increased from 36·5 kg. to 48 kg.

The adverse effects of sunlight and ultraviolet light on lupus erythematosus are well known. Radioiodine in therapeutic dosage appears to have had a similar activating influence and gave rise to an acute and progressive flare-up in this unrecognised case of systemic lupus.

In these two cases, the thyroid gland, although considerably enlarged, did not show the firm rubbery consistence of classical Hashimoto's disease. Unfortunately it was not possible to obtain needle biopsies of the glands.

In the presence of systemic lupus erythematosus the thyroid autoimmune reactions appears more likely to derive from a general disturbance of the homœostatic mechanisms regulating immune tolerance than to be a direct result of local thyroid dysfunction. One may perhaps envisage the existence of " lupoid thyroiditis ".

We wish to thank Dr. D. Doniach and Dr. I. M. Roitt, of the Middlesex Hospital, London, for performing the autoantibody tests on the two cases.

Department of Endocrinology, University Medical Clinic, Hôpital Brugmann, The Cesar De Paepe Clinic, Brussels, Belgium.

J. MAHAUX
J. DE PAEPE
J. P. NAETS.

RECENT ADVANCES IN PHRENOLOGY

SIR,—Perhaps you would allow me to comment on the most valuable and stimulating article by Dr. McFie (Aug. 12), in which he draws attention to the many valuable discoveries and theories of the old phrenologists.

For too long the lifework of one of the greatest anatomists and neurologists, Dr. Francis Joseph Gall, has been overlooked, ridiculed, and often grossly misrepresented and misunderstood. No doubt much of this has been due to ignorance, for many do not know of Gall's four-volume work *Anatomie et physiologie du système nerveux en général et du cerveau en particulier*, published in Paris between 1810 and 1819, together with a magnificent atlas of 100 engraved plates, which shows for the first time the true anatomy of the brain. Unfortunately this can now only be seen in museums (the British Museum has a copy).

Dr. McFie goes on to say: "The widest disagreements are on the localisation of intellectual functions . . . Without any measure of intelligence, and therefore without the means of establishing an association between lesions in different parts of the cerebrum and impairment of different aspects of intelligence, elaboration of these viewpoints [those of Goldstein, Henschen, and Marie] were little more than scholastic exercises." In connection with this and other special memory centres, he, together with other neurologists, seems to have overlooked the work of the late Dr. Bernard Hollander, who carried out fifteen years of research into this subject, described in his book *The Mental Functions of the Brain*, published in 1901. It contains material based on clinical and pathological investigations which would shed considerable light on present-day research. It seems extraordinary that such a valuable contribution has been so long ignored; but perhaps the intellectual climate when it appeared was inauspicious.

I hope that an impartial investigation, with modern methods, will be undertaken of the work of these pioneers in the localisation of mental functions, which was based not on intuition but on facts.

Ashford Common, Middlesex.

C. W. LE GRAND
Past President, British Phrenological Society.

NURSING CURRICULUM

SIR,—I am writing to ask you to give prominence to the changes about to be introduced by the General Nursing Council for England and Wales in their final examination for registration on the General part of the Register of Nurses.

The examination includes written, practical, and oral tests, of which the combined practical and oral examination is conducted entirely by nurse examiners. My only concern with it here is to note that the difficulty of enlisting a sufficient number of medical examiners interested in nursing education was one factor leading to the abandonment in 1950 of separate oral tests conducted by members of the medical profession.

The written part of the examination has hitherto consisted of three papers. In theory one paper is entirely confined to nursing, and the other two are based on medicine and surgery respectively as applied to nursing. In practice the distinction between these papers is hardly tenable, and for a long time it has been felt that nursing education should be directed towards eliminating such artificial divisions.

The present educational policy of the General Nursing Council recommends that an elementary course of lectures in medicine and surgery be given at the end of the first or the beginning of the second year of the student nurse's training, followed by a more specialised course later in the second or early in the third year. It is hoped that the subjects will be integrated with each other as far as possible, as well as with the teaching of actual nursing procedures and care of the patient, and ancillary matters such as dietetics. The occasional panel discussion would be ideal; sister tutor, dietitian, physician, and surgeon could, for example, cooperate advantageously in the teaching of peptic ulcer. Such a system is felt to be a great improvement on the traditional complete course of lectures in medicine or surgery, each given at an arbitrary period in the nurse's training, sometimes without correlation with her practical experience.

The changes being introduced into the written part of the final examination for State registration will embody these principles in two general papers set by an examining board of two nurse tutors, one physician, and one surgeon, and corrected by a panel of examiners drawn from both nursing and medical professions. One of the main purposes of this letter is to recruit additional examiners from the medical profession to the existing panel. This at present is composed largely of consultant physicians and surgeons, but with the more general nature of the papers in future the General Nursing Council would be glad to receive applications from a wider field. An interest in the teaching and training of nurses is the qualification most desired, and those who already participate in this training by giving lectures are of course particularly suitable. In all a medical panel of 170 is desirable, and those interested are asked to apply to the Registrar, General Nursing Council for England and Wales, P.O. Box 803, 23, Portland Place, London, W.1.

While putting this matter before the profession on behalf of the G.N.C. I would like to take the opportunity of adding a comment of my own. I would point out that, fortuitously these changes should to some extent mitigate the criticisms of the examination, not always well informed,

that have appeared in the medical press of recent years. I would add, however, that the majority of nurses are quite able to answer the questions which have been criticised as too academic. Perhaps some of these critics will apply for an examinership and, if appointed, change their view. In an age when the general public is educated in electroencephalography, in the constitution and behaviour of DNA, in the heart-lung machine, and in stereotactic operations for parkinsonism, to cite but a few, the nurse cannot be denied the knowledge she requires—for example, on the rectification of electrolytes, a matter she is handling daily. Indeed the nurse will not be denied, and that is the gist of the matter. I can none the less assure the critics that the practical nursing part of the examination carries the greatest weight and the largest proportion of marks, while no nurse is ever failed for want of abstruse academic knowledge. Moreover, for those, often good, practical nurses who find difficulty in answering a written paper, the State-enrolled nurse (S.E.N.) is slowly coming into her own.

MARGARET M. C. LOUDEN
Chairman of the board of examiners for the final general examination of the General Nursing Council for England and Wales.
Kenley, Surrey.

LOCAL AUTHORITY CLINICS

SIR,—May I express agreement with the letter from Dr. G. E. Crawford (Aug. 19)? By the same token, the Minister might well consider closing down that other institution which deprives the general practitioner of the opportunity of performing many of those duties for which he draws his pay—namely, the hospital casualty department. If these two ideas were executed the patient would be reduced to the hitherto unheard of position of having nowhere to go for medical attention but to his doctor!

Swansea. M. E. N. SMITH.

NUCLEAR SEX IN TRIPLOID XXY HUMAN CELLS

SIR,—In connection with the report by Professor Böök and Dr. Santesson (Aug. 5) on triploid XXY cells which were sex-chromatin-negative, we should like to record our findings on sex-chromatin in triploid cells.

A fœtus with 69 chromosomes, including XXY sex chromosomes, was described by Delhanty et al.[1] The triploid cells were present in cultures derived from yolk sac and from limb buds.

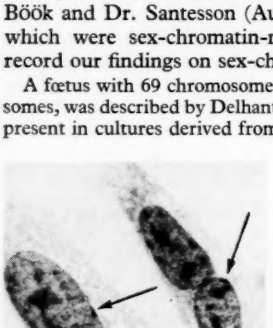

Fig. 1—Cells containing 1 sex-chromatin body.

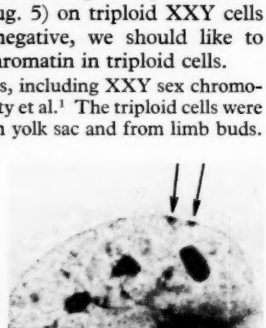

Fig. 2—Large cell (hexaploid?) containing 2 sex-chromatin bodies.

One of the cultures derived from yolk sac was stained with cresyl-fast violet after acid hydrolysis and examined for the presence of sex-chromatin. About a quarter of the cells were regarded as unclassifiable; of 200 cells which appeared suitable, 55 contained 1 sex-chromatin body (fig. 1). One large cell, which may have been hexaploid, contained 2 sex-chromatin bodies (fig. 2).

Galton Laboratory, University College, London W.C.1. URSULA MITTWOCH
JOY D. A. DELHANTY.

1. Delhanty, J. D. A., Ellis, J. R., Rowley, P. T. *Lancet*, 1961, i, 1286.

"J"-TYPE DIABETES

SIR,—I read with interest the paper by Dr. Tulloch and Dr. MacIntosh (July 15). I am inclined to agree with them that the "J" type is not a separate subgroup.

Control of the diabetic in the tropics is often difficult. A patient who has been stabilised in hospital on a certain dosage of insulin and an adequate calorie diet often finds it difficult to follow the treatment after discharge. He may live miles away from a dispensary or health centre where he could be given his daily dose of insulin. It is difficult to train the patients to give themselves insulin, as they are often unable to follow the instructions, or are not bold enough to prick their skin. The diet prescribed for them at the time of discharge is often not followed owing to lack of uniformity in dietary habits, ignorance of the caloric value of available foods, and poverty. The poor patient has to resort to cheap carbohydrates and cannot afford protein or fat. Most patients are unable to test their own urine, also because of ignorance and illiteracy. In our diabetic clinic we seldom find a patient's urine sugar-free when he returns after discharge from hospital. Some patients detest urine testing. Under these circumstances it is not surprising how badly diabetes is treated in the tropics.

I would be interested to know whether the subvariety described from Kampala [1] as diabetes-K, found in young persons with no tendency to ketosis who require low doses of insulin, is in fact only a subvariety or a form of type-II diabetes. Is it ever seen in the West Indies?

Central Hospital, Kumasi, Ghana. P. RABINDRAN.

"NO SPECIALISED EXPERIENCE"

SIR,—I should like to comment on a recent advertisement for a senior registrar and tutor in dermatology to a teaching hospital.[2] It was clearly stated that no specialised experience in dermatology was required. This mode of advertising appointments of senior dermatological registrars is not novel and reflects a retrograde trend.

Today the post of senior registrar is relatively permanent, and it is therefore incumbent upon those responsible for filling these posts to ensure that those appointed have had a suitable training in their chosen subject and will make good consultants in their specialty. How can this be accomplished if the candidate has no knowledge of his professed subject? Even more perplexing in the instance I quote is how the successful applicant could possibly be a tutor in a subject of which he is ignorant.

It has been argued that this means of attracting general physicians, at a late stage in their career, into dermatology is necessitated by the poor inflow of younger men at registrar level. If this is so, then it is a fault of our teaching, and our inability to stimulate interest in our subject. As long as dermatology is taught as a collection of impossible names relating to confusing eruptions, the modern well-trained medical student will reject dermatology as unworthy of his attention. Until we teach our subject on a dynamic and rational basis with reference to the anatomy, physiology, and pathology of the skin we will not attract the right type of recruit. It is imperative that medical men come into dermatology early in their careers as it is during these formative and progressive years that they will add their much-wanted contributions to their subject. The older, disillusioned, and rejected senior registrar in general medicine who is forced into dermatology by circumstances is most unlikely to bring the required enthusiasm, energy, and tenacity which our subject so desperately needs.

In addition, this initial recruitment of dermatologists at senior-registrar level lessens the chances of promotion for those already in training. This frustration further

1. Sharper, A. G. Proceedings of 3rd Congress of International Diabetes Federation. Dusseldorf, 1958.
2. *Lancet*, Aug. 19, 1961, advertisements p. 36.

reduces the intake at registrar level and greatly aggravates the shortage of applicants for registrar appointments. We must therefore not postpone the training of dermatologists beyond the registrar stage, for to do so is to endanger the future of British dermatology.

University College Hospital Medical School, London, W.C.1. A. JARRETT.

HOSPITAL DRUG COSTS

SIR,—In your annotation of Aug. 19 you state that joint purchasing schemes for drugs have been organised by regional hospital pharmaceutical committees and that it is because of the action of such committees that cheaper drugs are now obtainable. While, of course, it matters little who is given credit for such schemes it is, I feel, doing less than justice to the many hospital supplies officers who were often responsible for initiating joint contracting schemes for drugs and dressings at a time when some pharmacists were opposed to such action. Frequently now a joint committee of both pharmacists and supplies officers shoulder the not inconsiderable work that these joint contracting schemes involve.

North Middlesex Hospital, London, N.18. J. K. RHODEN.

TEACHING PSYCHIATRY

SIR,—May I support wholeheartedly the letter by Professor Neale (Aug. 19) on the teaching of psychiatry. We have implemented, or are implementing, his suggestions.

We have paid particular attention to providing really good residential accommodation. Our library is expanding rapidly and will shortly be moving into new quarters which will, indeed, be a quiet study room. The clinical seminars carried out by senior staff are a regular feature of the hospital life, as are clinical conferences. The hospital being organised into clinical teams, the junior doctor has the opportunity of informal teaching and supervision at outpatients as well as in the hospital. We are hoping that each team will eventually have three grades of junior doctor so that a young man on appointment can start as a senior house-officer and work up to registrar. During that period he can of course leave at any time and go into general practice or proceed to the D.P.M. We feel that we are now in a position to provide any junior with a comprehensive training in all aspects of basic psychiatry, and that partly owing to this we have been able to attract a good junior staff.

I think many of the teaching hospitals still do not realise the importance of psychiatry and are not positively encouraging young men to go into this expanding and worth-while field; and until they do, however much the psychiatric hospitals may attempt to provide good training and experience, the number and quality of applicants coming forward will be too low. I hope, therefore, that all who are concerned with the future of psychiatry will seriously consider Professor Neale's letter.

The Towers Hospital, Leicester. H. B. KIDD.

POLYLOGUE ON PRACTICE

SIR,—Your series on teaching of everyday psychiatry interested me as a general practitioner who is anxious to learn, for the management of psychiatric illness is one of the general practitioner's main problems. However, the only contribution relating directly to general practice was Polylogue on Practice (July 29), an account of a seminar attended by a number of general practitioners and a psychiatrist; and after all their discussion the doctors appear to have reached the not very original conclusion that a general practitioner is often upset when one of his patients dies.

Similar seminars have been meeting for years,[1] and apparently they discuss only details of psychotherapy and the handling of the doctor-patient relationship. Though psychotherapy is certainly valuable in general practice, it seems to me a pity that they confine themselves to this one aspect. Psychiatry in general practice bristles with unanswered questions, and they could profitably extend their range to include (1) the recognition of the common psychiatric syndromes and a study of their natural history, (2) an evaluation of modern methods of psychometry in general practice, (3) therapeutic techniques, including not only psychotherapy, but also conditioning, hypnosis, and the many new medicaments. They could undertake controlled studies in general practice both of these new drugs and of the established ones.

I am disappointed that your series of articles gave no indication that these developments are likely.

St. Paul's Cray, Kent. L. M. FRANKLIN.

HEPARIN LEVEL IN HÆMODIALYSIS

SIR,—At a discussion of hæmodialysis at the Glasgow Conference on Renal Disease in 1959, representatives of several artificial-kidney units in this country expressed the opinion that clotting in the artificial kidney was commoner when machines of large surface-area were used. This, they suggested, was probably due to adsorption of heparin on to the dialysing membrane. On this rationale we increased the administered dose of heparin when changing to a machine of larger surface-area, and we believe that this practice is fairly common. This probably has little significance in hæmodialysis of adults; but with small infants the addition of a few thousand extra units of heparin to " saturate the machine " might be hazardous if this in fact remained free in the blood. We carried out the following experiment:

20,000 units of heparin in 2 litres of physiological saline solution was passed through a standard ' Travenol ' twin-coil unit and recirculated for 6 hours. The measured levels of heparin in the solution were as follows:

Time	*Units per ml.*
Before circulation	$9{\cdot}96 \pm 0{\cdot}07$
After 5 minutes	$9{\cdot}99 \pm 0{\cdot}07$
After 4 hours	$9{\cdot}46 \pm 0{\cdot}07$
After 6 hours	$9{\cdot}50 \pm 0{\cdot}07$

Fluid lost by ultrafiltration was replaced to maintain the volume of the solution throughout as close as possible to 2 litres. It is, however, impossible to do so exactly, as the ' Cellophane ' tubing becomes slightly distorted when dialysis lasts several hours. The small changes in heparin level recorded are thus within the limits of experimental accuracy. It appears that heparin loss is not appreciable from a solution in contact with a cellophane membrane for the usual period of hæmodialysis. It has also been shown by static dialysis that no detectable amount is lost into the surrounding dialysing fluid.[2]

We therefore conclude that the dosage of heparin chosen in hæmodialysis should be based on the blood-volume of patient plus machine, without regard to the surface-area of the cellophane. When heparin dosage based on this assumption was selected for dialysis of a 15-month infant, we were not troubled by clotting in the machine.

We are grateful to Mr. J. Pritchard and Dr. C. H. Smith, of the Evans Biological Institute, Runcorn, Cheshire, for cooperation.

R. W. ELLIOTT
D. N. S. KERR
Royal Victoria Infirmary, Newcastle upon Tyne. D. T. PEARSON.

1. Balint, M. The Doctor, his Patient, and the Illness. London, 1957.
2. Pritchard, J. Personal communication, 1961.

INDUSTRY AND PROFESSION

SIR,—In your leading article of Aug. 19 you sound a note of warning lest the useful cooperation which exists between the medical profession and the pharmaceutical industry should degenerate into "a rather dangerous collaboration". In this country the industry has long recognised the necessity of preserving a good relationship with the medical profession of which it is, as you have acknowledged, an invaluable partner.

It cannot be said that in making donations for medical research or other medical causes or in enlisting the cooperation of members of the profession for the conduct of clinical trials, pharmaceutical manufacturers in this country have attempted to interfere with independent professional judgments. Manufacturers have also accepted voluntary control of sales promotion methods by supporting the Code of Practice operated by my Association, which is based on the principles (*a*) that the accuracy and completeness of the information given are of paramount importance, and (*b*) that promotion methods must be appropriate to the learning and professional status of the medical profession to whom they are directed. In view of the criticisms which have been made about the costs of medical literature and samples, it may be of interest to your readers to learn that the combined cost of these forms of sales promotion amounts to only 4·3% of manufacturers' net sales revenue.

Your correspondent in the same issue, writing on the situation in America, thinks it would be naïve to believe that the pharmaceutical industry exists in order to advance science, cure disease, or promote humanitarian good will; these, he writes, are only incidental by-products of their very clear and natural aim to make profits and sell their wares. The fact remains nevertheless that the industry exists and secures its reward in the form of profits only because, in partnership with the medical profession, it does achieve these results.

A. DUCKWORTH
Secretary, The Association of the British Pharmaceutical Industry.
London, W.C.1.

SIR,—In neither of the valuable articles in your issue of Aug. 19, nor in many others I have read on the same theme, is it made sufficiently clear that the present position is developing largely through doctors' apathy.

It is good that competition in the pharmaceutical industry should make all firms adopt progressive methods in order to survive, but it leads some to be more aggressive than is desirable in medicine. If it should prove that the firms using the least desirable methods are the ones that prosper most, the others will be obliged to follow suit and a further deterioration of standards will ensue. Firms are, however, sensitive to criticism, and doctors who resent their methods should refuse to see their representatives, ask to be deleted from their mailing list, and refrain from prescribing their products. Doing nothing is tacit acceptance.

The second most common type of criticism concerns the conduct and adequacy of clinical trials—in fact the part of the process of drug development that still remains the profession's responsibility.

No reputable firm nowadays wants to market preparations of less clinical value than those already available. They realise that early and accurate clinical reports are in their own best interests, and will do their utmost to encourage objective trials. It is now highly probable that, if a drug is marketed without adequate trial, the fault lies more with the profession than with the industry; for the small minority of doctors able and willing to undertake this work are overburdened—partly because they have to do it as a spare-time hobby. The more querulous majority does not give them due credit for evaluating the promising newcomers; still less for eliminating many others that never appear at all. Nor has it faced the fact that improved facilities for testing and reporting are urgently needed in order to keep pace with the increasing number of potential new drugs.

Fortunately, one can still believe what one reads in British journals. There are occasional black sheep, who are prepared to compromise their professional integrity for personal gain, but they are quickly recognisable. Their conduct is no less infamous than some of the misdemeanours that are reported in your columns and they should be dealt with in the same way.

The pattern of the relationship between industry and the profession is clearly being shaped for the future. It seems to me that in every country the profession gets the industry it deserves.

T. B. BINNS.
Pinner, Middlesex.

SIR,—The article entitled "The Pharmaceutical Persuaders" in *The Lancet* for Aug. 19 contains much with which one can agree; indeed, all of the author's remarks about preclinical toxicity testing can be accepted with no more than an expression of surprise that he should have felt it necessary to make them. It is my impression that many companies go further, insisting not only that primates should be among the experimental animals used, but that human tolerance should be determined in healthy volunteers before administering a new drug for the treatment of the sick.

As regards "persuasion", the author seems to be confusing the setting up of clinical trials of an experimental drug with the promotion of a new product. The latter is no concern of mine, but in initiating clinical trials any form of persuasion is best avoided; my own belief is that in order of their importance the qualities required of an investigator are interest, time, and facilities. If he is interested in the proposed project no persuasion is needed, and if he is not we would not wish to persuade him. For this reason it is my practice to stress the difficulties of the proposed investigation and the known toxic and side effects of the drug to be tested rather than its unique advantages, which are, of course, indicated in the pharmacological data which I present to the potential investigator. In this way I hope to ensure that no clinician undertakes a trial in which he has no real interest. Remuneration is, of course, *never* mentioned by me, though I make it clear that the company will meet any essential expenses. Should the clinician himself bring up the question of a "research grant" my usual reaction is to seek another investigator, for payment does not ensure interest and may well excite suspicion in those to whom the worker's results are presented. Once an investigator has agreed to undertake a trial the only influence which one can legitimately bring to bear is influence towards conducting the trial in such a way as to eliminate the possibility of bias.

It is not apparently clear to your anonymous correspondent that the interest of a pharmaceutical company is best served by impartial, objective reports upon their experimental products and that nothing could be more disastrous than a fallaciously favourable report leading to the marketing of a useless or dangerous product. By the time the mistake is discovered very large sums may have been spent on plant and advertising, almost all of which will be wasted.

The analysis of results by a statistician employed by the company is a service which we offer to our investigators and which they frequently accept. It had never occurred to me until your correspondent voiced suspicions on the subject that this practice could be open to misinterpretation; I am sure our investigators who have made use of our statistical department will be equally surprised at this. It would, in fact, be simple

to keep the statistician in ignorance of the particular medications given to the various treatment groups in a double-blind study, and we once did this but have not ordinarily considered it necessary.

We always request, though we never insist upon, a prior view of draft papers intended for publication. The only purpose of this is to correct any errors of fact which may be present, particularly in the sections dealing with chemistry and pharmacology. At the same time we check any calculations the paper may contain and examine the validity of conclusions based on statistical analysis unless carried out by professional statisticians of known competence. No pressure is *ever* brought to bear upon an investigator *not* to publish his results, and the reason why those published are predominantly favourable is because journals usually reject reports of entirely negative trials. The exception is when such a report contradicts what may be a falsely favourable previous one.

In conclusion, the publication of your anonymous correspondent's article might possibly have some point in his own country, though it is my impression that the leading companies in the United States accept the same principles and standards of behaviour as obtain here, but its publication in Britain constitutes a disservice not only to the pharmaceutical industry, whose efforts to carry out honest clinical trials already meet with more than enough difficulties (as you admit in your leader in the same issue) but also to the medical profession and their patients, whose interests are best served by making new drugs available to them backed by solid clinical evidence as to effectiveness and necessary precautions with a minimum of delay.

J. A. L. GORRINGE
Director,
Department of Clinical Investigation.
Parke, Davis & Company,
Hounslow, Middlesex.

SIR,—Your editorial and the special article on The Pharmaceutical Persuaders draw timely attention to the ethical dangers inherent for both parties in our present modus vivendi with the drug industry.

As the Inland Revenue treats selling costs (i.e., advertising in all forms) as if they were genuine production costs, the more the industry spends on advertisement the less it is required to pay in tax. Hence the inordinate spate of competitive sales pressure in every fantastic form to which we are daily subjected.

$750 million annual expenditure on advertising in the United States provides an approximate clue to expenditure by the industry in this country.

As all costs are embodied in prices, and as the Ministry of Health provides a guaranteed home market and purchases about 90% of the ethical products of the industry, the Minister of Health is himself responsible for squandering the British equivalent of $750 million public money on sales expenditure which is grossly extravagant, largely redundant, and as you, Sir, point out, ethically dangerous.

Either to impose a strict statutory limit on permitted advertising expenditure, with a corresponding price reduction by any drug house whose products are recognised by the Ministry, or to impose a tax on all income accruing to a firm not offset by genuine costs of production or research; these alternative ways are open to the Minister, the one of decreasing expenditure, the other of increasing revenue. With such a measure he would take a decisive step to end the present mésalliance between industry and profession which, to judge from reports of sessions of the Kefauver Committee (U.S. Senate), is becoming ominously akin to a racket.

As the co-author of the socioeconomic work, *The Social Services—Means and Needs*, the Minister must discern clearly the salient features of a situation which could receive adequate justice only from the late W. S. Gilbert.

ALLAN CHATELIER.
London, S.E.13.

SIR,—Your exhaustive discussion (Aug. 19) of our attitude towards the pharmaceutical persuaders prompts me to publish the results of some researches.

After (1) enthusiastic collection, (2) destruction unread, and (3) laborious sorting of wheat from chaff, a colleague at this hospital and I, noticing that a suggestion made in 1957 had caused a few firms to issue standard E.C.6-size ($7/^1_8$ in. $\times$ 5 in.) cards, began collecting them in a card-index.

Requests to all the other firms brought us nearly three feet of well-written cards, describing nearly every ethical proprietary in greater detail than the drug journals' cards. We now destroy with a clear conscience all polychromic literature (except French Impressionists and Old Masters, which my wife collects); and we tell representatives that we need no more information. Yet are these cards not cheaper than "traditional" advertising?

The cards were, it seems, originally made to file at the ends of E.C.6 drawers; but to allow filing in the wallets of patients on the respective drugs, some were altered to E.C.7 size (7in. $\times$ $4^1/_2$ in). Taller cards were thought to be advantageous, until some became too tall to file.

Several firms have found the perfect method: loose-leaf catalogues made up of standard cards, serving the needs of doctor, pharmacist, and representative alike. One firm issues E.C.6-size brochures, wasting file space with blank covers. Only one firm absolutely refuses to issue cards; the few others which issue no cards as yet are considering doing so. In many cases the cards are apparently available only on request.

One firm asked me for suggestions, and I made a list. While no one firm gives all these details, each item is listed by several: (1) standard size (E.C.6?), thin card, double if needed; (2) trade name at top lefthand corner; (3) maker's name or trademark alongside; (4) three or four descriptive words in large type; (5) approved name and composition; (6) pharmacological properties; (7) indications; (8) contraindications; (9) side-effects; (10) toxicity to man, antidotes; (11) dose; (12) presentation; (13) administration, storage, &c.; (14) packs; (15) prices; (16) reference to animal tests, clinical trials, &c.; (17) date of introduction, former names, &c.; (18) illustration of tablets, for identification; (19) blank space at top righthand corner for private index headings; (20) multiple presentations of the same drug on one card, to save repetition; (21) maker's full address (sometimes omitted on loose-leaf pages); (22) date of issue of card, in simple code if preferred.

The following details, included by some firms, do not seem strictly necessary:

1. Lengthy chemical details, including methods of manufacture.
2. Full details of animal tests. (Your American correspondent [Aug. 19] was writing of drugs undergoing clinical trial; I am concerned with drugs on general sale.)
3. Full details of clinical trials; the data should be used to provide items 8–10 above.
4. Long descriptions of standard remedies: textbooks are the place for them.

The level to aim at should be that of the junior consultant, well-grounded in medicine. He wants to know whether a new drug will help his patient and how to give it. He wants neither a tutorial on sedatives nor a research fellowship in pharmacology.

ROBERT J. HETHERINGTON.
Summerfield Hospital,
Birmingham.

SIR,—As one of the band of medical representatives referred to in your correspondent's article, I am increasingly incensed by articles and statements which depict my job as that of a man who forces himself on unwilling doctors and then persuades them to prescribe useless drugs.

This article places us in a very poor light and also, I fear, infers a poor degree of intelligence and integrity on behalf of the doctor. Articles about so-called high-pressure salesmanship seem anxious to protect a rather simple physician who

prescribes useless drugs on the instructions of a representative. I have never met this type of doctor.

The article and accompanying leader have the now familiar implication of sharp practice in the pharmaceutical industry, and the representative once again comes in for an attack. There have been many similar articles in other publications, yet I still receive a friendly welcome from my doctor contacts whenever I call. I wonder if the loudest critics of the medical representative are not totally ignorant of his relationship with the doctor.

Representatives are not psychologists adept at mind manipulation, indeed, it is the doctor who has had this training. I feel a person would need to be exceptionally skilful to influence psychologists. This we are not, and to me it does not seem reasonable to suggest this. Providing we are always completely honest, the doctor is likely to try products for the recommended conditions. In this way sales materialise and our employers are satisfied, but first and foremost, representatives of my acquaintance are always true to themselves.

Nobody objects to a technical representative from a company such as Rolls-Royce talking to an aeroplane company about jet engines. Similarly, I would expect that nobody would object to my talking to any medical man about my company's products. Strangely they seem to. Can anyone tell me why?

London, W.8. M. C. WILLIAMS.

α-HYDROXYBUTYRIC DEHYDROGENASE IN THE DETECTION OF MYOCARDIAL INFARCTION

SIR,—Of the measurements of serum enzyme activity, determinations of glutamic oxalacetic transaminase (G.O.T.) and lactic dehydrogenase (L.D.) have been found the most practical as an aid to the detection of myocardial infarction. But an increase in these enzyme activities is by no means certain evidence of myocardial infarction.

It is indeed possible to differentiate organ-specific isoenzymes of L.D. and so get further information about the origin of enzymes appearing in serum; but the separation of these enzymes is too laborious for clinical use. Sometimes, moreover, serum lactic dehydrogenase can be non-specifically elevated to a pathological level—e.g., by vigorous physical exercise.[1] What is needed, therefore, is a more specific and simple diagnostic reaction for myocardial infarction. As the concentration of the enzyme which reduces α-ketobutyrate to α-hydroxybutyrate seems to be greater in the heart tissue than in the liver, we may expect it to be more specific for myocardial infarction than, for example, L.D. or G.O.T. The preliminary report of Elliott and Wilkinson,[2] who called this enzyme α-hydroxybutyric dehydrogenase, supports this.

I have studied the activity of α-hydroxybutyric dehydrogenase (H.B.D.) in fresh myocardial infarction, in angina pectoris, in liver diseases, and in apparently healthy men.

The enzyme was determined as by Elliott and Wilkinson. The substrate in the reaction—the sodium salt of α-ketobutyric acid—was prepared by precipitating it with ether from the alcohol solution of α-ketobutyric acid and 10 *N* sodium hydroxide. The solution contained equimolar amounts of α-ketobutyric acid and sodium hydroxide. The salt was then washed with ether and dried. For the comparison, the activities of G.O.T. and L.D. were determined from the same serum samples. The results are presented in the table.

The normal range of α-hydroxybutyric dehydrogenase seems to be up to 300 or perhaps 350 units. (One unit is a spectrophotometric change of 0·001 in optical density at 340 mμ per min.) The material presented here, however, is too small to warrant conclusions. In cases of myocardial infarction H.B.D. was elevated in every one of the 30 cases studied. G.O.T. was not elevated in 6 cases and L.D. was false-negative 5 times. In angina pectoris, both G.O.T. and L.D. were positive once. H.B.D. was once doubtfully positive (327). In the 27 cases of liver diseases G.O.T. was elevated in 21 and L.D. in 9; but H.B.D. was only once clearly elevated though in 3 cases it was between 300 and 354 units. The liver diseases were a heterogeneous group of occlusive icterus, metastatic liver damage, liver cirrhosis, and hepatitis.

Thus H.B.D. seemed to be more specific for myocardial infarction than G.O.T. or L.D. On many occasions when both the latter were considerably raised, H.B.D. was normal or even subnormal. Statistically, there is no difference between myocardial infarction and the liver-diseases group in the reaction of G.O.T. or L.D., but in the reaction of H.B.D. the difference between these groups is highly significant ($P < 0.001$).

One drawback to the use of G.O.T. is its rapid return to the normal level—perhaps even before the patient enters hospital. But H.B.D. activity, though it seems to rise promptly, remains raised for 3 or 4 days longer, corresponding in this respect to L.D. and glucose-6-phosphate dehydrogenase.[3]

The determination of H.B.D. is even simpler than, for instance, that of G.O.T. Further study, however, will be needed before final conclusions can be drawn as to its suitability for practical purposes.

Wihuri Research Institute, Helsinki, Finland. AARNE KONTTINEN.

1. Halonen, P., Konttinen, A. (to be published).
2. Elliott, B. A., Wilkinson, J. H. *Lancet*, 1961, i, 698.

ENZYME ACTIVITIES IN DIFFERENT GROUPS OF PATIENTS

Group	Number of cases	G.O.T. (units per ml.)		L.D. (units per ml.)		H.B.D. (units per ml.)	
		Mean ± S.E.	Range	Mean ± S.E.	Range	Mean ± S.E.	Range
Myocardial infarctions	30	105 ± 12·3	(23–258)	1021 ± 109·9	(202–2290)	793 ± 75·0	(391–1890)
Angina pectoris	31	22 ± 1·9	(11–64)	280 ± 21·6	(86–747)	180 ± 10·2	(84–327)
Liver diseases	27	113 ± 20·3	(21–502)	588 ± 196·2	(76–5550)	179 ± 22·7	(18–612)
Healthy men	20	16 ± 1·0	(9–26)	234 ± 15·1	(174–388)	132 ± 6·4	(104–186)

3. Kerppola, W., Nikkilä, E. A., Pitkänen, E. *Acta med. scand.* 1960, **166**, 17.

YOUR HEART

SIR,—I have just been reading the review of the book *Your Heart* which appeared last week. Though I agree that this book is an excellent one of its kind, I have some doubt about the desirability of writing "popular" books on disease.

From the point of view of the doctor treating a patient with heart-disease, such a book may well make the patient unduly critical of the efforts to help him (however well directed they are) if they fail to come up to expectations aroused by reading the merits of all the possible lines of treatment outlined in the book. On the other hand, the patient who reads the book may be dismayed by all the possible errors in diagnosis and treatment which the doctor may commit. In the end, I suppose, the patients and doctors who see eye to eye about matters in the book relevant to the patient's disease will get together and live happily; but I foresee that the path to this symbiosis may be difficult. Although in a general way we may condemn ignorance, the fact remains that not all patients have the

necessary background of wisdom and knowledge to read such a thorough account of a fatal disease without developing all sorts of imaginary symptoms and anxieties.

I fear very much that this book may, in spite of the author's warning, become a substitute for the advice of a physician.

Eridge, Sussex. F. J. PRIME.

MANAGEMENT EFFICIENCY IN THE HEALTH SERVICE

SIR,—It was refreshing to read Dr. Seale's paper of Aug. 26. He criticises rightly the present system of managing the Health Service which results in those in power at the centre being ignorant of its day-to-day running yet being forced by M.P.s' questions to direct their attention to technical details and away from major strategic issues. Equally true is his statement that the centralised control of finance is a serious cause of delay and drains responsibility from the rest of the service so that it is difficult to attract staff to work with hospital management committees that have little authority.

Dr. Seale's proposals on finance are matters on which he must speak with hesitation, for they belong to a specialised field; the idea of a special tax recalls the Road Fund which did not survive long as a separate entity. His proposals on administration are matters of immediate concern and are topical in view of the activities of the Local Government Commission. Dr. Seale rightly states that if recommendations or change are required, they must be communicated to relevant persons in such a way that they are accepted, and appropriate action is taken. The first relevant person to be considered is the man in the street, who is a more caustic critic than most members of our profession seem to realise, and he is not likely to favour special taxes, new community health boards, and paid representatives serving on them. These suggestions might have been acceptable 15 years ago, but experience since then does not commend them to him now.

A system which would produce no less effective results and be acceptable to the people who are to pay for it was outlined in *The Lancet* last year,[1] and Dr. Seale would be more likely to achieve his end by using existing organisations.

Wolverhampton. J. F. GALLOWAY.

SIR,—Once more Dr. Seale (Aug. 26) has given us a most informed exposé of what is required in the sound management of a Health Service; and it is to be hoped that the Minister's advisory council takes heed of what he says. But one thing strikes me as unsaid (perhaps because Dr. Seale is too tactful)—how does the service rid itself of its inefficient members?

In industry, the running of a department can be investigated and the site of the lesion determined. An inefficient manager can be transferred to a less important section on the grounds that his "ability" is required there. At board level, a director can simply be dismissed. How are we to implement this in a Health Service? If we want to have an efficient one, it is essential that some machinery should exist to relieve it of its poorer elements. No department is healthy in which the head does not enjoy the confidence of the subordinates.

The Minister is in no position to know what goes on in the diagnostic room or in the operating-theatre. The patient comes blind to the hospital. He has not the slightest notion of the quality of his medical attendant. The truth is known only to the medical and nursing staff of the hospital. We can all think of the intriguant who has literally bought his way into a hospital in the pre-National-Health-Service days. He may be, say, a surgeon who, through the dictum that "those who can, operate; and those who can't become chairmen of committees", has wormed his way to an important "managerial" level. Yet such a person's crapulence is only second to the poor quality of his surgery. How is he to be removed? Neither his pseudo-loyal colleagues (who secretly dread falling ill on his duty week!) nor the nursing staff can oust him. Short of gross negligence he could not be relieved of his appointment. In the meantime the "product" suffers, and the "objective" is lost—and no redress exists. There seems to be only one solution to this problem: an official non-Ministerial board of inquiry with powers to investigate the working of any one clinical unit. Only then can qualitative data be assessed and translated quantitatively. Could such a board be part of the permanent institute Dr. Seale suggests?

1. *Lancet*, 1960, ii, 34.

London, W.6. L. R. CELESTIN.

DRUG ADDICTION

SIR,—I should like to reply to Dr. Stungo's letter (Aug. 19).

The late Dr. Philip Hamill taught me, as I remember, that the addict required the drug for his normal metabolism; hence the withdrawal symptoms. I blame myself for lack of clarity, if Dr. Stungo did not perceive my plea to abolish the unnecessary distinction between "habituation" and "addiction". He condemns himself in two phrases: ". . . certain psychopathic types abuse them", and ". . . the former [i.e., his addicts] cannot lead normal existences even with their drug."

I offer this definition: "A person who depends on drugs for continued apparent mental health, and who shows withdrawal symptoms of varying degree on ceasing to take them." And this I would apply equally to the addict to smoking, alcohol, aspirin, or heroin. I regard Dr. Stungo's "addict" (in his final paragraph) as an addict with a psychopathic overlay.

Cardiff. H. CAIRNS.

ADMITTING SCHIZOPHRENIC MOTHERS WITH THEIR BABIES

SIR,—Dr. Martin (Aug. 19) has raised several queries about our article on schizophrenic mothers.[1]

This particular research is one of a number of interrelated research projects which have been described in more detail elsewhere.[2–4] Briefly, no patient was included in our report unless schizophrenia had been definitely diagnosed by an outside consultant psychiatrist as well as two psychiatrists at this hospital. In practice this means that the patients described have had either a florid or a longstanding schizophrenic illness. Affective illnesses have been excluded.

The control group was treated at this hospital between 1956 and 1958 inclusive, and the unit patients between 1959 and 1960. The period of stay of this type of patient had already decreased at this hospital by 1956; and both groups were treated under the same consultant's guidance with the object of returning them home as soon as possible. Review of their histories suggests that the longer stay by the control group was largely due to the anxiety and uncertainty which developed when the schizophrenic mother returned home to her baby and found they were strangers to each other. We did not consider that the ability of the mother to look after her baby on discharge was the primary consideration in assessing results. Many looked after their babies very well throughout their stay even when obviously psychotic. As our table showed, the symptom rating on the Wittenborn rating-scale confirmed our impression that the mothers treated with their babies had fewer symptoms on discharge than the group treated without their babies.

We entirely agree with Dr. Martin that the prognosis for patients with a schizophrenic illness in the puerperium should

1. Baker, A. A., Morison, M., Game, J. A., Thorpe, J. G. *Lancet*, July 29, 1961, p. 237.
2. Baker, A. A., Game, J. A., Thorpe, J. G. *J. ment. Sci.* 1960, **106**, 203.
3. Baker, A. A., Bird, G., Lavin, N. I., Thorpe, J. G. *ibid.* p. 1506.
4. Baker, A. A., Game, J. A., Thorpe, J. G. *ibid.* 1958, **104**, 860.

be good. Unfortunately this is not as yet generally accepted. We still have patients referred to us from other hospitals where they and their relatives have been given a bad prognosis.

We think, on the evidence available, that the onus of proof now lies with those who wish to separate mother and baby. Has anyone shown that this really benefits either when the mother has a schizophrenic illness?

Downview and Banstead Hospitals, Sutton, Surrey. A. A. BAKER.

5-HYDROXYTRYPTAMINE AND MULTIPLE SCLEROSIS

SIR,—While investigating the 5-hydroxytryptamine content of different biological fluids, using Vane's biological assay method,[1] we tested a sample of cerebrospinal fluid taken from a patient with multiple sclerosis. It was shown that an acetone extract [2] of this fluid relaxed the rat gastric fundus used in this assay.

We assayed samples of cerebrospinal fluid from 4 patients with multiple sclerosis at different stages of their disease. On three occasions we could not find any 5-hydroxytryptamine in the extracts; in one experiment there were some minute contractions of the strip of rat gastric fundus, but not enough to enable the 5-hydroxytryptamine content to be assayed. In 1 case we observed a decreased reactivity of the rat gastric fundus to standard doses of 5-hydroxytryptamine after consecutive additions to the bath fluid of cerebrospinal fluid extracts. In the serum of these 4 patients the 5-hydroxytryptamine level was very low.

In acetone extracts of the cerebrospinal fluid in 3 patients with neurological disorders but with no symptoms of multiple sclerosis, we could easily detect 5-hydroxytryptamine in amounts similar to those usually reported. Extracts of the cerebrospinal fluid of these patients caused a typical contraction of an isolated strip of rat gastric fundus, which was completely inhibited by a serotonin antagonist 1-methyl-*d*-lysergic acid butanolamide tartrate ('Deseril', UML-491, Sandoz).

Further investigations are in progress and experimental details will be published shortly. We are indebted to Professor Chłopicki for kindly supplying samples for assay.

Department of Pharmacology, Silesian School of Medicine, Zabrze, and Department of Pharmacology, School of Medicine, Białystok, Poland. ZBIGNIEW HERMAN ANDRZEJ DANYSZ.

DRUG-INDUCED GASTROINTESTINAL BLEEDING

SIR,—We were interested to read your leading article last week in which you were kind enough to quote work from this department. We have continued to study the problem of salicylate-induced bleeding, and so perhaps you will allow us to make a few comments.

You would counsel patients with peptic ulcers against taking aspirin for the relief of incidental discomfort. This is commonsense advice, but we must stress that there is no published evidence that the tendency to peptic ulceration and the tendency to bleed after taking aspirin are in any way related. We have compared the blood-loss caused by aspirin in 56 patients with a peptic ulcer, past or present, with the loss observed in 194 patients with no evidence of an ulcer tendency (and in 76 of whom results of a barium meal were normal). There was no significant difference between the two groups. We have already drawn attention to the lack of association between dyspepsia and occult bleeding after aspirin ingestion. Aspirin is a very valuable drug for patients with rheumatic diseases, and we do not think that it should automatically be withheld from those who also have a peptic-ulcer history.

We should also like to stress that the evidence implicating aspirin as a cause of major gastrointestinal hæmorrhage is largely circumstantial. We have had the opportunity of studying a few patients who presented with hæmatemesis or melæna, who had recently taken aspirin, and who had no history of previous dyspepsia. On clinical grounds such an episode might readily be attributed to aspirin. We commenced our studies within a short time of the hæmorrhage, and it was striking that some of these patients did not bleed after taking further aspirin. Our material is at present insufficient to justify firm conclusions. It may be that the bleeding phenomenon we have observed is unrelated to major hæmorrhage. But we wish to plead for caution in too readily implicating aspirin as a common cause of major hæmorrhage solely on circumstantial evidence.

Postgraduate Medical School, London, W.12. PHILIP H. N. WOOD J. T. SCOTT A. ST. J. DIXON.

1. Vane, J. R. *Brit. J. Pharmacol.* 1957, **12**, 344.
2. Amin, A. H., Crawford, T. B. B., Gaddum, J. H. *J. Physiol.* 1954, **126**, 596.

Obituary

SINCLAIR MILLER

D.S.O., M.C., M.A., M.D., B.Sc. Belf., M.R.C.P., D.P.H.

Dr. Sinclair Miller, who died in Harrogate on Aug. 24 at the age of 76, contributed notably to medical practice in Harrogate and a wide area around, first by detecting the emerging importance of clinical pathology when this was evident to few, secondly by building up a pathological service which in some respects was the envy of much larger centres, and finally by encouraging practitioners, through his informed enthusiasm, to use this service to the best advantage.

He graduated M.A. with honours at Belfast in 1910, and B.SC. with first-class honours in 1912; and he qualified M.B. in 1914. In the 1914–18 war he served with distinction in the R.A.M.C., gaining the rank of lieut.-colonel and being awarded the D.S.O. and bar and M.C.

In 1919 he settled in Harrogate, where he was appointed pathologist to the Royal Bath Hospital and the Infirmary (now the General Hospital). For some years the pathological work of these and other hospitals was undertaken at a private laboratory which Dr. Miller ran, initially in association with Dr. F. B. Smith. Not only Harrogate hospitals but others—notably at Ripon and Ilkley—benefited by the high standard of this laboratory; and the blood-transfusion service which he started some ten years later was far in advance of its time. He graduated M.D. with commendation in 1922 and took the M.R.C.P. in 1929.

In 1924, together with one or two colleagues, Dr. Miller opened an investigation clinic, which he continued to run until a few years ago. This, backed by an efficient clinical-pathological service, offered to patients a standard rarely achieved outside large general hospitals.

A colleague writes:

"Harrogate was fortunate to have attracted a man of Dr. Miller's calibre. In his work he was indefatigable, driving himself (and his car) with unflagging vigour. He was always interested, always up to date, and always unassuming: when in 1929, after no perceptible interruption of his crowded routine, he slipped up to London and came back with the M.R.C.P. he refused to concede that he had done anything out of the ordinary. He was a skilled organiser; for otherwise he could not have run an outstanding pathological service, controlled a clinic whose organisation seemed as smooth as that of a teaching hospital, engaged in private practice, and at the same time kept up with his reading. Outside his work his life was centred on his family, and on his garden to which he would devote half an hour each morning at a time when most of his fellows

were stirring to hark to the cock crow. He was a man of exceptional talent; and, unlike some talented people, he used his gifts fully."

Dr. Miller married in 1915 Norah Isabel, daughter of R. G. Blendinning, P.C., M.P., who died in 1954. In 1958 he married Mrs. Isabel Wales Dick. He is survived by his widow, two sons, one of whom is a consultant physician at Bedford, and a daughter, who is in practice at Caerphilly.

JAMES THORNTON SMALLEY
M.R.C.S.

Dr. J. T. Smalley, a former senior medical officer in the Colonial Service, died in Cambridge on Aug. 17.

The son of the late Major-General F. Smalley, he qualified in 1907 from Guy's Hospital and held a house appointment there before he joined the Colonial Medical Service. After some years' work in Fiji he was posted to Hong Kong where he found time, despite a large surgical practice, to lecture on jurisprudence and materia medica and pharmacology in the university.

P. M.-B. writes:

"James Smalley was almost the first to greet us when my wife and I stepped ashore on Fiji in January, 1910. He himself had only been there a short time, but long enough to prove that he was an outstanding surgeon. Of fine physique and commanding appearance, with a brisk and decisive manner, he bore the stamp of his military ancestry. He was a very good friend to me and tireless in his efforts to promote my research on filariasis. One of the puzzling problems of those days was the number of Polynesians with hip-joint disease. Till then the condition had been treated as tuberculosis of the hip. It was not long before Smalley had operated on four of them and asked me to make a pathological investigation. He proved that the trouble was due to septic infection of the hip-joint, secondary to inflamed filariated inguinal lymphatic glands which had been invaded by streptococci. Removal of these and drainage of the synovial cavity proved successful, and ankylosis no longer ensued."

JOHN MILBURN MOUNSEY
M.B. Dubl., D.C.H.

Dr. J. M. Mounsey, who served for 26 years as school medical officer for Portsmouth, died in the Queen Alexandra Hospital, Cosham, on Aug. 13 after a short illness. He was 64 years of age and was due to retire in six weeks' time.

Born in Sheffield, Mounsey moved in early childhood to Dublin when his father, an accountant, was transferred there, and he was educated at the High School and Trinity College, where he won a Fitzpatrick scholarship. After graduating M.B. in 1923, he spent two years at the Dublin Medical Mission studying tropical medicine, for he hoped to become a medical missionary, but his wife's health prevented this. His interest in children's diseases was encouraged by his experience as house-surgeon at the Royal Alexandra Hospital for Children, Brighton, and the Royal National Orthopædic Hospital, London, and in 1931 he was appointed school medical officer at Portsmouth. He remained in this post except for a period in Northampton and in general practice at Southbourne during the late war.

R. E. R. writes:

"Possessed of deep religious convictions, Mounsey gave much of his leisure to Church work, and his high moral standards and integrity were evident in the meticulous care he devoted to the examination of the children for whom he was responsible. Because of his clinical acumen his advice was often sought by his colleagues."

Dr. Mounsey leaves a widow.

Notes and News

ROYAL COLLEGE OF SURGEONS OF EDINBURGH

Surgeon's Hall has been the home of the College since 1832 and, apart from one enlargement in 1908, it has remained unchanged. With the years, administration, library, museum, and journal have all found themselves cramped and a major scheme of expansion and reconstruction has now been carried out which provides more space and yet respects Playfair's neo-classic building. The administrative offices of the college (and of the Central Midwives' Board) and the journal have been moved to a building in Hill Square which is joined to Surgeons' Hall by a new office entrance which has a frontage of glass in a teak frame. With the space thus gained in the old building a long vaulted reading-room and a council room have been formed out of former offices and storerooms. The main museum remains practically as Playfair designed it, with its original fittings and furniture. A large hitherto unfloored basement area has been lined, ventilated, and lit, and now provides cloakrooms and generous storage for the library, with which it is connected with a lift. The old building and the new meet, at the new office entrance, in a vaulted lobby to the council room. The junction is a glazed frame through which the viewer may contrast the classical and modern styles.

COMMUNITY MENTAL CARE

SOME of the many difficulties that stand in the way of developing community care are brought out by the 1960 report of Fulbourn Hospital, Cambridge. Throughout the National Health Service there is a gulf between hospital facilities (in which national pressure promotes uniformity) and the services which are locally financed and therefore vary widely. While the work of all the professional people trying to help a patient should be complementary, some of them are in fact often unaware of what the others are doing, and need constant ingenuity to keep in touch. "In planning, the division is more crippling; local health authority and hospital areas seldom coincide; methods of financing are different and ancient animosities crop up only too easily." Fulbourn provides psychiatric cover for a city, three administrative counties, and parts of three others, with a total population of 260,000. In the whole area, local government is threatened with reorganisation, and this is said to have had "a most unfortunate and unsettling effect on the development of a mental health service".

Certainly, it seems easiest to develop an integrated community service in a compact urban area, and this has no doubt contributed to the success of the experiments at Oldham and Nottingham. (The London conurbation, with its shifting population, many local authorities, and peripheral clusters of large mental hospitals, may represent a problem almost insoluble under present conditions.) Nevertheless, the achievement at York of coordination among a variety of authorities suggests that, where there is the will to cooperate, a whole jungle of administrative complications may be overcome.[1] In rural West Sussex too, the services based on Graylingwell Hospital have made much progress through a positive community orientation, though they have not emphasised cooperation with the local health authority.

This emphasis is clearly evident, however, in the even more rural area served by Fulbourn. Cambridgeshire has been unusual in that its aftercare services for mental health have been delegated since 1948 to the local mental-welfare association. In 1960 the services were reorganised under a joint committee representing hospital and local authority. The mental-welfare officers each undertook to provide a complete mental-health service for his sub-area, based on the needs of the family and dealing with both the subnormal and the mentally ill; and regular meetings have been arranged to coordinate their work with that of the hospital staff. But in other parts of the country the preference has been for distributing social workers on a functional rather than geographical basis, or for

1. Crane, C. B. Address to Royal Society of Health congress, 1960.

attaching them to clinical teams within the psychiatric hospital. The valuable part which the mental-welfare officer can play in relation to the psychiatric outpatient clinic has already been emphasised in the Cambridge region.[2] Fulbourn operates six clinics, including an emergency service at the general hospital; they had a total attendance of over 15,000 in 1960, and provided a major part of its total psychiatric service. Another valuable facility is the now well-known Winston House halfway hostel[3]; 20 patients from Fulbourn went there during the year, and many of these were long-stay cases. This confirms the now general impression that the demand for short-stay hostel accommodation is extremely limited.

Altogether, this report indicates a vigorous therapeutic programme within the hospital, which represents an essential basis for community care outside.

G.P.s AS HOSPITAL LOCUMS

IN the Birmingham region, as elsewhere, hospitals are often short of junior medical staff, and last May the regional board asked the local executive councils if some general practitioners would be willing to act as hospital locums. The scheme would provide useful hospital experience for the practitioners and help the hospitals by filling urgent vacancies, even if only for short periods. Payment would be made not on the clinical assistantship scale but on the usual hospital scale (ranging from £14 10s. per week for a house-officer to £32 per week for a senior registrar).

On inquiry the Birmingham executive council found that 36 general practitioners were already attending hospitals on a sessional basis; but a further 28 have volunteered to support the new scheme and act as occasional hospital locums.

SALARIES AT CAMBRIDGE

THIS week we publish an advertisement for a university assistant biochemist at Cambridge. In doing so, we would remind readers[4] that Cambridge University differs from other universities in its payment of medical members of the teaching staff. As a result of the decision, last February, of the regent house at Cambridge no longer to make differential payments to clinical teachers, the British Medical Association decided that, as things stand, it cannot advertise medical or other appointments in the university.

University of Bristol

Dr. W. A. Gillespie, lecturer in clinical bacteriology in the university and consultant pathologist to the United Bristol Hospitals, has been appointed to the newly established part-time chair in clinical bacteriology at the university.

Dr. Gillespie, who is 49 years of age, was educated in Dublin at St. Andrew's College and Trinity College. After qualifying in 1936 he held appointments in the department of pathology and bacteriology at Trinity College. In 1938 he was awarded the Adrian Stokes fellowship and the same year took the D.P.H. After spending a year in the Emergency Medical Service in this country he served from 1943 to 1947 as a pathologist in the R.A.M.C. On demobilisation he took up his present appointments. He was elected F.R.C.P.I. in 1957. His published work includes papers on the sterilisation of dressings and hospital cross-infection.

University of Hong Kong

Dr. C. Elaine Field, at present temporary consultant pædiatrician in the South Manchester hospital group, has been appointed to the chair of pædiatrics in the university. She has held an appointment as a pædiatric specialist in Singapore.

Bureau of Hygiene and Tropical Diseases

Dr. Charles Wilcocks is to retire on Nov. 30 from the post of director of this bureau. He joined the bureau as assistant director in 1938 and was appointed director in 1942. He will be succeeded by Dr. H. J. O'D. Burke-Gaffney, who has been assistant director since 1946.

2. Pargiter, R. A., Hodgson, T. D. *Lancet*, 1959, ii, 727.
3. Clark, D. H., Cooper, L. W. *ibid.* 1960, i, 588.
4. See *Lancet*, 1961, i, 1122.

British Congress on the History of Medicine and Pharmacy

Chemistry in the Service of Medicine has been chosen as the theme of this congress which is to be held in London from Sept. 27 to 29 under the presidency of Prof. Douglas McKie. Further particulars may be had from Dr. F. N. L. Poynter, Wellcome Historical Medical Library, The Wellcome Building, Euston Road, London, N.W.1.

International Congress on Diseases of the Chest

This congress, sponsored by the Council on International Affairs of the American College of Chest Physicians, will be held, under the auspices of the University of Delhi, the Indian Association for Chest Diseases, and the Vallabhbhai Patel Chest Institute, from Feb. 20 to 24, 1963, in New Delhi. Particulars may be had from the American College of Chest Physicians, 112, East Chestnut Street, Chicago 11, Illinois.

Commonwealth Health and Tuberculosis Conference

The Chest and Heart Association is to hold the next of this series of conferences at University College, Ibadan, from March 26 to 31, 1962. A limited number of places will be available to delegates from the United Kingdom. The inclusive cost (to cover return air fare, accommodation, and meals in a university hostel) will be £135. Further particulars can be had from the Association, at Tavistock House North, Tavistock Square, London, W.C.1.

Lord Taylor will give the inaugural address to St. George's Hospital Medical School on Friday, Sept. 29, at 3 P.M. at Agricultural House, Knightsbridge.

Sir Stanford Cade has been appointed a member of the advisory committee on the administration of the Cruelty to Animals Act 1876 in place of Sir Geoffrey Keynes who has resigned.

Dr. W. D. Buchanan has been appointed a member of the Ministry of Labour's Joint Standing Committee on Health, Safety, and Welfare in Non-Ferrous Foundries.

Prof. Mario d'Almeida, who holds the only chair of anæsthetics in South America, has been appointed an honorary C.B.E. He has done postgraduate work in the departments of anæsthetics at the London Hospital and Oxford, and he was the first South American to be awarded the F.F.A. R.C.S. During the war years, and since, he has done valuable work for the British community in Rio de Janeiro.

The British Council for the Welfare of Spastics have published the addresses given last December at their conference on mentally subnormal spastics. Copies (4*s.* 6*d.* post free) may be had from the Council, 13, Suffolk Street, London, S.W.1.

The Ministry of Health's Hospital Building Bulletin no. 2 deals with accommodation for nursing staff. Copies (3*s.* net) may be had from H.M. Stationery Office. The *Bulletins* are intended to supplement with fuller details the Ministry's *Building Notes*. *Bulletin no. 1* dealt with operating-theatres.

The 1961 *Register of Medical Auxiliary Operating Theatre Technicians* has been published by the Board of Registration of Medical Auxiliaries. Copies of the register will be sent free to members of the medical profession, hospitals, and official bodies on application to the registrar of the board, B.M.A. House, Tavistock Square, London, W.C.1.

Appointments

DAVIS, P. R. H., M.R.C.S., D.P.M.: consultant psychiatrist, Reading area department of psychological medicine for duties at Fair Mile Hospital.
ROWLAND, A. J., M.B. Brist., D.OBST., D.P.H.: assistant M.O., Worcestershire.
SANDERSON, K. V., M.B. Adelaide, M.R.A.C.P.: consultant physician for diseases of the skin, St. George's Hospital, London.
SIPPERT, ALAN, M.B. Manc., D.P.H.: deputy M.O.H., Wigan.
STOKOE, I. H., M.D. Edin., M.R.C.P.: assistant physician in geriatrics (S.H.M.O.), based on Southfield Hospital, Edinburgh.

Births, Marriages, Deaths

DEATHS

MILLER.—On Aug. 24, at his home, Pinewood Lodge, 71, Cornwall Road, Harrogate, Yorks, Sinclair Miller, D.S.O., M.C., M.A., M.D., M.R.C.P., D.P.H.